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INDIAN MEDICAL ASSOCIATION

VOLUME 24 NUMBER 13 CALCUTTA APRIL 1, 1955

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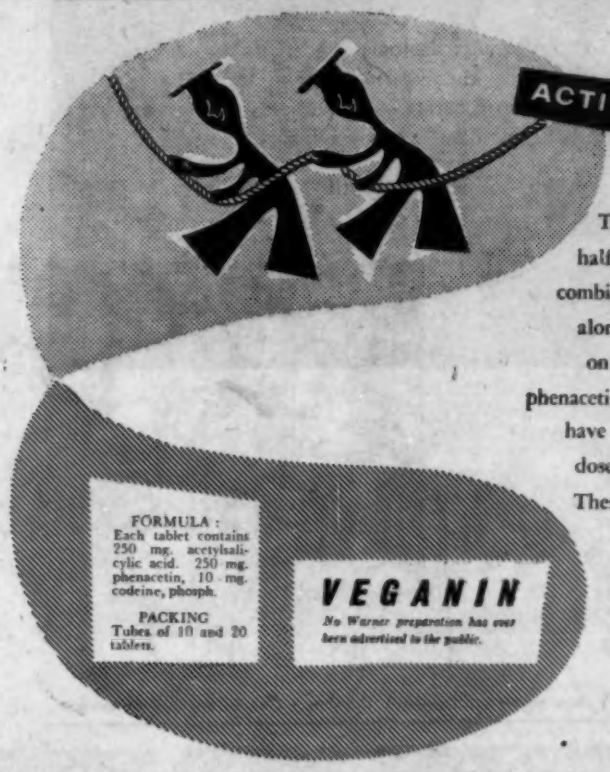
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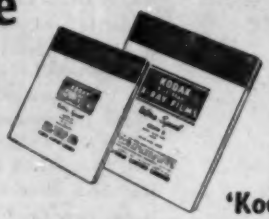

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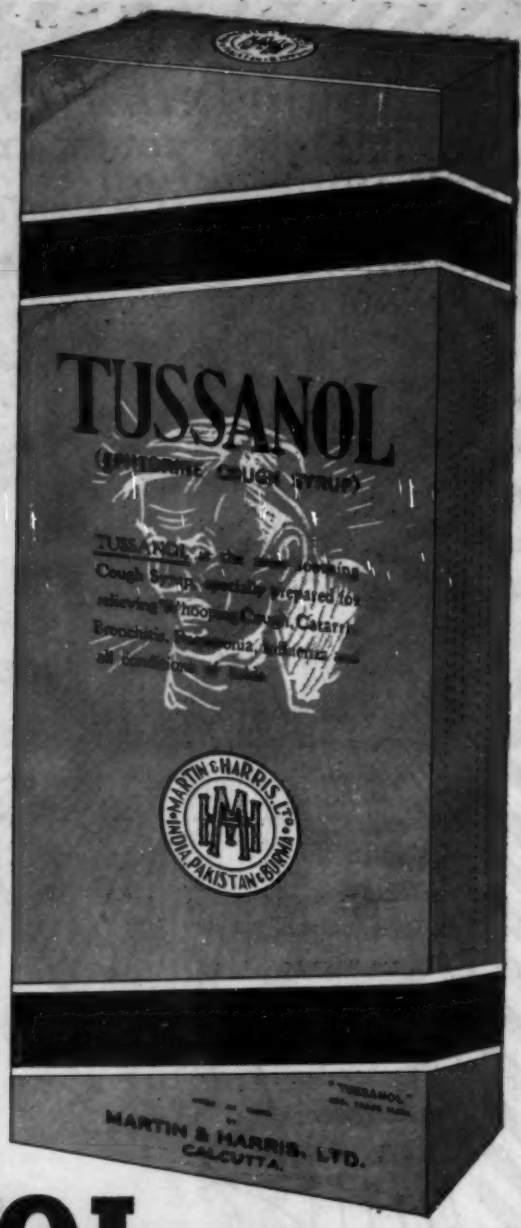

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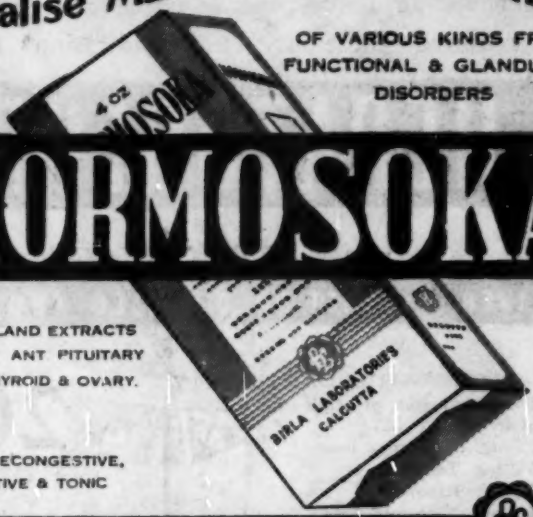

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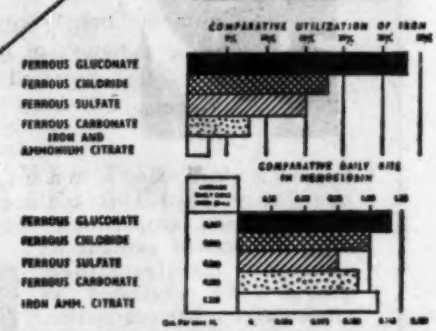

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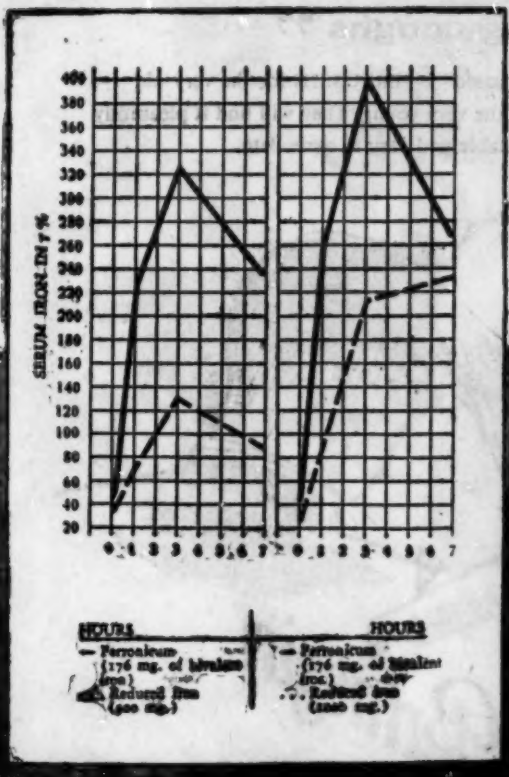

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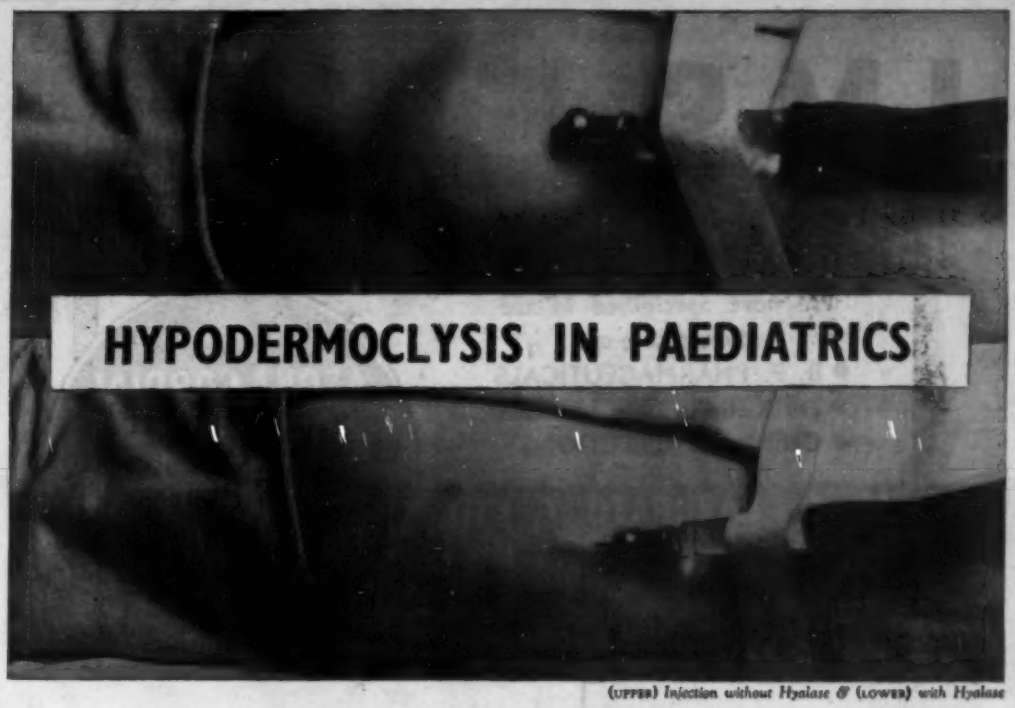

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ORIGINAL ARTICLES

GLOSSITIS RHOMBICA MEDIANA: A LESION CONFUSED WITH CARCINOMA

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Glossitis rhombica mediana, otherwise called median rhomboid glossitis is a rare condition, and is probably of congenital origin. It is a benign lesion of the tongue, characterised by the presence of a plaque, located anterior to the circumvallate papillae of the tongue. Martin and Howe (1938) have stated, that this anomaly is connected with the triangular tuberculum impar, which forms the pharyngeal floor between the first pair of bronchial arches, and have given a comprehensive review of the literature on the subject.

During the last 13 years, 6 cases of glossitis rhombica mediana, were seen at the Tata Memorial Hospital, Bombay. Table 1 gives relevant data concerning these 6 cases. Detailed case histories are not given because all of them closely resemble one another and are not dissimilar to the descriptions in the literature. One case (Case 5) however, is reported below in detail to illustrate the lesion fully.

Case Report

A Hindu male aged 35, (No. P. 4253) was admitted to the Tata Memorial Hospital, Bombay, on August 8, 1954, for an oval nodular swelling, on the dorsum of the tongue. The nodule was located anterior to the circumvallate papillae and measured 3×2 cm. Shallow fissures traversed its surface (Fig. 1, *vide* Plate). It was painless. There was no evidence of leukoplakia, either associated with the lesion, or in any other part of the mouth. The submaxillary lymph nodes were palpable on both the sides. The patient was referred to the hospital with a tentative diagnosis of carcinoma of the tongue. The blood serologic test for syphilis was negative.

A biopsy was done. The following histologic features were observed: the tissue was covered over by stratified squamous epithelium. There was marked hyperplasia of the surface epithelium. The cords of the epithelial cells were tangentially cut and were scattered in the subepithelial area. Throughout, the cells were, however, well differentiated. There was moderate subepithelial lymphocytic infiltration (Fig. 3, *vide* Plate). The microscopic characters did not show evidence of malignancy in any portion of the biopsy specimen.

Since the cervical lymph nodes were enlarged, one of them was also removed for microscopic examination. It showed characters of chronic simple adenitis. The patient was assured that this was a benign condition and told that no treatment was necessary.

Comment

All the 6 cases were referred with a tentative diagnosis of carcinoma of the tongue. The lesions were clinically diagnosed as glossitis rhombica mediana. The diagnosis was based on the gross features and the characteristic position of the lesion. The lesion in each of the 6 cases was either an oval, or a rhomboid plaque, or a nodular swelling rising 4-5 mm. over the dorsum of the tongue. It was painless and the surface was smooth and glistening. It had a very characteristic position: middle line of the tongue, anterior to the circumvallate papillae. This area seems amazingly immune from a primary carcinoma. In 2,000 cases of carcinomas of the tongue Martin and Howe (*loc. cit.*) failed to discover a single instance of a malignant growth located in this area. At the Tata Memorial Hospital also, in a series of 4,400 carcinomas of the

TABLE I—SUMMARY OF DATA IN 6 CASES OF GLOSSITIS RHOMBICA MEDIANA

Serial No.	Age	Sex	Duration	Clinical findings
1	32	M	1 year	A raised protuberance, rhomboid in shape, at the apex of circumvallate papillae on the dorsum of the tongue.
2	41	M	1½ months	An oval plaque on dorsum of the tongue, granular feel.
3	39	M	1½ months	An oval plaque denuded of epithelium, anterior to the circumvallate papillae on the dorsum of the tongue.
4	26	M	10 years	A rhomboid elevated area, anterior to the circumvallate papillae on the dorsum of the tongue. Firm to feel.
5	35	M	20 days	A nodule on the dorsum of the tongue, submandibular lymph nodes, palpable on both sides.
6	50	F	2½ months	A nodule on the middle of the tongue.

tongue, there was not a single instance in which a carcinoma was seen arising primarily in this area.

A biopsy was performed on all 6 cases; primarily for confirming the clinical diagnosis and also for excluding the possibility of malignancy. In all 6 cases, the microscopic examination substantiated the clinical diagnosis and in none was there any evidence of a malignant change. In 5 cases the histological findings were uniform. Microscopic examination showed stratified squamous epithelium on the surface. There was acanthosis and hyperplasia of the epithelium with subepithelial round cell infiltration. Subepithelial fibrosis extending into the muscular layer was a characteristic feature of the condition (Fig. 2, *vide* Plate). The case reported above, however, showed a somewhat different histological appearance. In this instance the epithelial growth was quite exuberant and there were cords of epithelial cells beneath which were interpreted as resulting from the tangential cut of the section. Nowhere was there any evidence of an anaplasia. To an unwary such an appearance may suggest a mistaken diagnosis of a carcinoma.

Martin and Howe (*loc. cit.*) have stated that no treatment is indicated in cases of glossitis rhombica mediana, except in patients who have a cancerophobia. If the patient demands removal of the lesion, surgical excision is the method of choice. In the present series, no treatment was given, the patients being reassured that the lesion was benign.

SUMMARY

1. Data concerning 6 cases of glossitis rhombica mediana are presented in a tabular form. One case is described in detail.

2. In all the cases a diagnosis of glossitis rhombica mediana was made on clinical examination and substantiated by microscopic examination.

3. The significance of the lesion lies in the fact, that though a benign lesion it is frequently confused with carcinoma.

4. The gross features and microscopic characters of the lesion are described in detail.

5. It is generally accepted that no treatment is indicated for this lesion.

REFERENCE

MARTIN, H. E. AND HOWE, M. E.—*Ann. Surg.*, **107**: 39, 1938.

SINGLE DOSE TREATMENT OF MALARIA

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AND

B. N. DUTTA, M.SC.,

From the School of Tropical Medicine, Calcutta.

The standard treatment of an acute attack of malaria is to give an antimalarial drug, taking about 3 to 10 days according to the nature of the drug used, during which time it is administered daily in divided doses. Such a course of treatment aiming to kill the asexual parasites in the blood as far as possible is not convenient for the vast majority of the poor and ignorant people living in remote villages far from hospitals, whilst being frequently exposed to fresh infection. A more simple, yet clinically effective form of treatment would be a boon to these people, as malaria being the commonest disease of rural areas in India interferes greatly with their daily occupation. The idea of a single dose treatment of malaria was first suggested when during investigation of the action of proguanil it was observed that one dose of 300 mg. could achieve a clinical cure, and it began to take a definite shape when later more potent drugs were discovered (Fairley *et al*, 1946; Afridi, 1947; Chaudhuri and Rai Chaudhuri, 1947; De and

Datta, 1947a, 1947b ; Ghosh, 1947 ; Gupta, 1954 ; Lomax, 1947 ; Jafar, 1947 ; Parekh and Boghani, 1947a, 1947b ; Srivastava, 1947). During the last 8 years we have used a number of synthetic antimalarial remedies in single doses in the treatment and prophylaxis of malaria among semi-immune people in the hospital as well as in the field, and we here record how this knowledge can be applied particularly to village conditions. The essence of the treatment consists in giving one dose of the chosen drug to effect a clinical cure, and in following it up with a weekly or fortnightly dose to suppress relapses or fresh infections. The drugs tested were proguanil, mepacrine, chloroquine, 7 - chloro - 4 - (3-dimethylaminomethyl-4-hydroxyanilino) quinoline and pyrimethamine.

Proguanil—Even as early as 1946 we had started a pilot study of proguanil in different single dose regimens, results of which have been published (Chaudhuri and Rai Chaudhuri, 1947). The immediate effect on the temperature and asexual parasites is shown in Table 1. A dose of 0·1 g. was unsatisfactory, while 0·3 g. to 0·5 g. was more promising, but a higher dose has not been of any advantage either in controlling the acute attack or in preventing the relapses. Moreover, with such a high dose as 0·8 g., toxic reactions such as gastro-intestinal irritation with nausea, vomiting, diarrhoea and renal irritation were experienced (Chaudhuri, 1948 ; Chaudhuri *et al*, 1952). The action of the drug was slow and occasionally cases failed to respond even in repeated doses ; this therapy is therefore, not suitable for acute cases of malaria. We also tried proguanil lactate by I.V. injection, it had no advantage over oral therapy. Besides it was not quite safe (Chaudhuri and Chakravarty, 1949).

Mepacrine—Its reputation was well established during the last war, but because of occasional toxic manifestations mostly as a result of large doses and of the advent of newer antimalarials it came to be neglected and its use in malaria was about to be forgotten. We have shown that for the Indian civilian population a four-day course of 1·5 g. is sufficient and that there is no need for massive dosage like 2·7 to 3·0 g. as was common in military practice (Chaudhuri, 1948 ; Committee on Chemotherapy, C. S. I. R., 1949). When it was found that a single dose of chloroquine (0·4 to 0·6 g. base) was almost as effective for immediate clinical cure as 1·2 to 1·5 g. of the same drug given in 3 days (Chaudhuri, Rai Chaudhuri and Chakravarty, 1948; Chaudhuri and Chakravarty, 1948 ; Chaudhuri and Dutta, 1950 ; Chaudhuri, 1954a) we thought that mepacrine, having similar pharmacological property in that it is slowly excreted from the body, might act in more or less the same way and be equally effective in single doses (Chaudhuri, 1953, 1954b ; Chaudhuri, Saha and Chakravarty, 1954 ; W.H.O. 1954). Accordingly we tried the drug, so far on 70 patients of different ages, 10 of whom had falciparum, 59 vivax and 1 mixed infection. The following dosage was used in most cases up to 2 years—

TABLE 1—EFFECT OF SINGLE DOSE TREATMENT WITH DIFFERENT ANTIMALARIALS ON FEVER AND ASEXUAL PARASITES.

Drug & Dose	Number of cases					Fever subsided				Asexual parasites disappeared			
	Total	F	V	M	FV	Within 2 days		In 3 or more days		Within 2 days		In 3 or more days	
PROGUANIL						No.	per cent	No.	per cent	No.	per cent	No.	per cent
0·1 g.	11	7	2	1	1	4	36·4	7	63·6	7	63·6	4	36·4
0·3 g.	42	26	16	—	—	22	52·4	20	47·6	28	66·6	14	33·4
0·5 g.	25	12	12	—	1	11	44·0	14	56·0	18	72·0	7	28·0
0·6—0·8 g.	12	6	6	—	—	6	50·0	6	50·0	5	58·3	7	41·7
MEPACRINE													
0·6 g.	70	10	59	–	1	62	88·6	8	11·4	61	87·1	9	12·9
CHLOROQUINE													
0·6 g. base	95	48	46	1	—	80	84·2	15	15·8	91	95·8	4	4·2
7 CHLORO-4 (3-DIETHYL-AMINOMETHYL-4-HYDROXY-ANILINO) QUINOLINE													
0·6 g. base	104	42	46	10	6	90	86·5	14	13·5	94	90·4	10	9·6
PYRIMETHAMINE													
50—100 mg. ...	80	39*	37	4	—	41	51·2	57	46·2	51	63·7	27	33·7

*2 cases did not respond and early recrudescences were observed in 12 cases.

0·1 g., 2-5 years—0·2 g., 6-12 years—0·4 g. and above 12 years—0·6 g. In as much as 88 per cent cases fever subsided and parasites disappeared in two days and in the rest within 3 or 4 days. (Figs. 1 and 2). Of the 21 patients followed up,

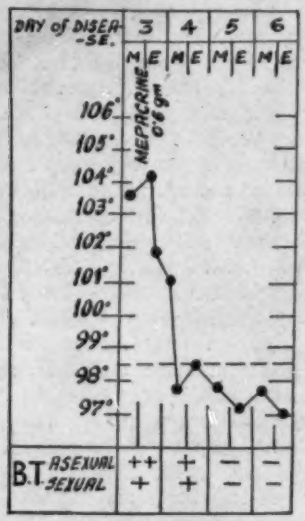
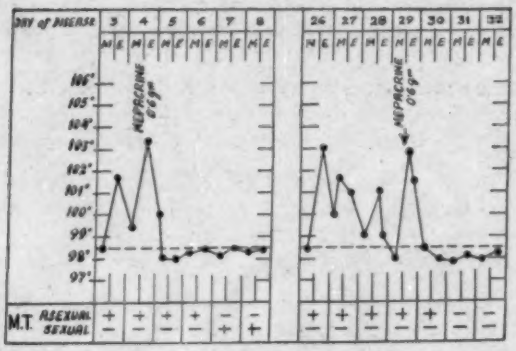


FIG. 1—VIVAX MALARIA TREATED WITH SINGLE DOSE OF 0·6 G. OF MEPACRINE.


DAY of DISEASE
3 4 5 6 7 8 26 27 28 29 30 31 32
M E M E M E M E M E M E M E M E M E M E M E M E M E
MEPACRINE 0·6 gm
MEPACRINE 0·6 gm
106°
105°
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103°
102°
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M.T. ASEXUAL + + + + — —
SEXUAL — — — — + +
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— — — — — —

FIG. 2—FALCIPARUM MALARIA TREATED WITH SINGLE DOSE OF MEPACRINE. RELAPSE AFTER 19 DAYS—TREATED WITH MEPACRINE 0·6 G. IN SINGLE DOSE.

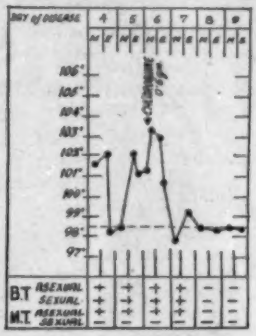

FIG. 3—MIXED INFECTION (FALCIPARUM AND VIVAX) TREATED WITH SINGLE DOSE OF 0·6 G. OF CHLOROQUINE.

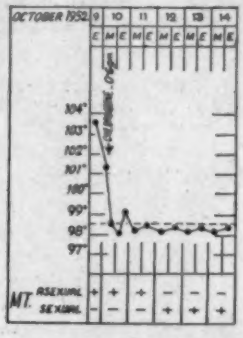

FIG. 4—FALCIPARUM MALARIA TREATED WITH SINGLE DOSE OF 0·6 G. OF CHLOROQUINE.

seven vivax patients relapsed, four after 3-5 weeks, and three after 8 months. No untoward reaction was observed with this dosage. Incidentally, it may be mentioned that one patient passed a tapeworm after the dose.

Chloroquine—When chloroquine was introduced into the therapeutics of malaria the dose recommended by the Board of Malarial Studies and different authorities was a total of 1·5 g. base to be given in 3-4 days (Loeb *et al*, 1946 ; Most *et al*, 1946 ; Berliner, 1948 ; Coggeshall, 1952 ; United States Army, 1947a, 1947b ; W.H.O., 1949). Successful results obtained with single dose treatment of the drug 0·5-0·6 g. was first reported by us in 1948 from India (Chaudhuri, Rai Chaudhuri and Chakravarty, 1948) and by other workers abroad (Halawani and Baz, 1950 and Penido, de Sousa and Bezerra, 1948). Children were given ⅓ to ¼th the adult dose. This single dose treatment with chloroquine has become so popular and so efficacious that many physicians in endemic areas now prefer it to the longer course with divided doses. In 10 per cent of our cases the latter dosage caused untoward reactions such as insomnia, gastro-intestinal irritation, pruritus (especially in the hands and feet) and pain in the lower abdomen, gonads, and thigh, but these usually disappeared in two days. One patient had epileptic form convulsions (Chaudhuri *et al*, 1950, 1952). The effect of chloroquine on the disappearance of parasites and fever is shown in Table 1 which indicates that with 0·6 g. single dose in a series of 95 cases of malaria the asexual parasites disappeared from the peripheral blood within 2 days after treatment in 95·8 per cent cases and the fever subsided in 84·2 per cent of cases within the same period (Figs. 3 and 4). No untoward reaction was encountered and there was no failure.

7 chloro-4-(3-diethylaminomethyl-4-hydroxyanilino) quinoline—Efficacy of single dose treatment was first reported from India (Simeons and Chhatre, 1947 ; Chaudhuri and Chakravarty, 1948). A single dose of 0·5 g. brought about a clinical cure and appeared superior to 0·6 g. in divided doses (0·1 g. twice daily for 3 days). The drug was also used in dosages varying from 0·25 g. to 1·0 g. (Simeons and Chhatre, 1947 ; Chaudhuri and

Chakravarty, 1948 ; Patel and Mehta, 1948 ; Mein, 1948 ; Deane, 1948 ; Hamilton, 1950 ; Hoekenga, 1950 and 1951 ; Wallace, 1951 ; Khatri and Samuels, 1953 ; Singh, Misra and Ray, 1953). While a dose of 0·25 g. had comparatively slow action, a single dose of 0·6 g. was effective, which has been recommended as the standard form of therapy by different authorities. We used the drug in single doses of 0·6 g. in a further series of 104 malaria cases, 42 of whom had falciparum, 46 vivax, 10 malariae and 6 mixed infections (3 falciparum and vivax, 3 falciparum and malariae infections). Children were given ½ to 2/3rd the adult dose. The results shown in the table indicate that fever subsided in 86·5 per cent cases and asexual parasites disappeared in 90·4 per cent cases within 2 days of treatment. In the rest, the asexual parasites disappeared and fever subsided usually within 3 days. The drug was well tolerated and no untoward reactions were noticed even in cases of severe anaemia.

Pyrimethamine—This was introduced into the therapeutics of malaria when it was shown that a single dose of 25 mg. would effect clinical cure (Schneider *et al*, 1952 ; Schneider, Montezin and Bihen, 1952a and 1952b ; Archibald, 1951; McGregor and Smith, 1952). Similar trials of the drug were conducted in India and elsewhere (Chaudhuri, 1953 ; Chakravarty and Chaudhuri, 1953 ; Laha, Singhal and Navani, 1953 ; Khatri and Samuels, 1953 ; Srivastava, Chakraborty and Mukherjee, 1953 ; Wilson and Edeson, 1953). Pyrimethamine in dosages of 50-100 mg. was used by us in 80 malaria cases of whom 39 had falciparum, 37 vivax and 4 malariae infections. The drug was first used in single doses of 50 mg. in 19 cases but this was found ineffective in some and hence two such doses were given on consecutive days in the remaining cases. Children were given ½ to ¼th the adult dose. Fever subsided in 51·2 per cent and asexual parasites disappeared in 63·7 per cent of cases within 2 days. The drug proved slower in action than 4-aminoquinoline group and mepacrine. The immediate effects on the disappearance of parasites and fever are shown in Table 1. Two cases of falciparum failed to respond to a dose of 50 mg. even when it was repeated 24 hours later and 12 others had early recurrence within 1-2 weeks. It, therefore, does not appear suitable for the treatment of falciparum malaria. However, it was effective in two or three days' time in case of vivax and malariae infections. No toxic symptoms were noticed with this dosage.

Suppression of Further Attack

Relapses would inevitably occur at different intervals after such treatment but usually not before 3 or more weeks after mepacrine or 4-aminoquinolines. In order to prevent these relapses the patients should be kept under suppressive medication. Before or during the war years, in a malarious endemic area, almost daily dose of quinine or mepacrine was recommended for this purpose (Field, Niven and Hodgkin, 1937 ; League of Nations, 1937 ; Covell, 1943 ; Adhikari, 1947). But this is an impracticable method specially in civil practice. It was later demonstrated that a weekly dose of newer drug is quite sufficient to suppress the infection. In this respect weekly administration of chloroquine (0·25 to 0·3 g. base), 7 chloro-4(3-diethylaminomethyl-4-hydroxyanilino) quinoline (0·2 g. base), proguanil (salt, 0·3 g.) or pyrimethamine (25-50 mg.) was found to afford high protection and reduce splenomegaly, thereby improving the general health of the population and increasing the working capacity, (Chaudhuri, 1947, 1948, 1949, 1950, 1951, 1952, 1953, 1954a, 1954c ; Chaudhuri and Poti, 1950 ; Chaudhuri *et al*, 1952 ; Goldsmith, 146 ; Ray, 1948 ; Adhikari and Ganguli, 1952 ; Singh, Misra and Ray, 1953). Further advance was made when it was found that even a fortnightly dose of 7 chloro-4(3-diethylaminomethyl-4-hydroxyanilino) quinoline (0·4 g.), chloroquine (0·4 to 0·6 g.) can produce about the same result (Chaudhuri and Chakravarty, 1952; Chaudhuri, 1952, 1953 ; Singh *et al*, 1953 ; DeSmet, 1953). An increase of the intervals of these medications has obvious advantages and the premunition of the host may be allowed to exert its maximum role in the fight against malaria. The suppressive action of mepacrine is well-known, but we are trying by field experiments to determine the intervals at which it can be administered with best results. The results of a preliminary trial, now in progress, with fortnightly doses of 0·4 g. of mepacrine have so far been encouraging.

Discussion

Our experiments with proguanil some 8 years ago to find out a single dose treatment of malaria were not as successful as we had hoped owing to slow action of the drug, and occasional resistant cases that were subsequently encountered (Chaudhuri, 1948 ; Chaudhuri and Rai Chaudhuri, 1949; Covell *et al*, 1949 ; Covell, 1951 and 1953 ; Edeson and Field, 1950 ; Gilroy, 1952a, 1952b ; Norman, 1953a and 1953b ; Ferro Luzzi, 1948). Soon after chloroquine was introduced we found that the recommended dose of 1·5 g. over 3 days was rather higher than is really necessary for average malaria, and that less than half this amount could be given in a single dose with equally good and immediate effect clinically (Chaudhuri, Rai Chaudhuri and

Chakravarty, 1948 ; Khan *et al*, 1952 ; Patel and Mehta, 1948 ; Hamilton, 1950 ; Scheele, 1953 ; Bruce-Chwatt and Archibald, 1953). The same proved to be the case with 7 chloro 4(3-diethyl-aminomethyl-4-hydroxyanilino) quinoline (Wallace, 1951 ; Laufer and Freedman, 1953 ; Bruce-Chwatt and Archibald, 1953 ; Khan *et al*, 1951 ; Patel and Dalal, 1954 ; Simeons and Chhatre, 1947 ; Khatri and Samuels, 1953 ; Mein, 1948 ; Deane, 1948 ; Hoekenga, 1950 & 1951 ; Chaudhuri, and Chakravarty, 1948). Both drugs are highly effective and have powerful schizonticidal effects in single doses of 0·4 to 0·6 g. The difference between therapeutic efficacy of chloroquine and 7 chloro-4(3-diethylaminomethyl-4-hydroxyanilino) quinoline is marginal, though some investigators are in favour of chloroquine, while some have spoken of the superiority of the other (Singh and Kalyanum, 1952 ; Gauld and Houel, 1953). Occasional failures with single doses of 4-aminoquinolines have however been reported from Africa, necessitating the administration of other antimalarial drugs like quinine (Messent, 1951 ; Lauffer and Freedman, 1953 ; Gauld and Houel, 1953 ; Goodwin, 1952).

In single dose therapy one should guard against the possibility of the patient having vomited it out in which case this can be safe-guarded to a large extent if the patients attending the out-patients or rural clinic are made to take the tablets in the presence of the attending physician and wait for some time. In any case the dose has to be repeated, if vomited out. The 4-aminoquinolines are very effective but they are relatively costly. In this respect mepacrine is much cheaper (a single dose of 0·6 g. costing now about 1½ anna) and possesses at the same time similar pharmacological properties and almost similar antimalarial activity. In view of this it is not surprising that a single dose of mepacrine, 0·6 g., can effect clinical cure of malaria among semi-immune population. Every case having single dose therapy should however, be kept under observation or instructed to report for at least 2 days after the dose. For a severely ill patient or non-immune subject the full treatment preferably with quinine is obviously indicated. As an alternative to single dose treatment of malaria, quinine should be used for treatment of malaria in doses of 5 gr. t.d.s. for 5 days in villages. Quinine may be combined with 8-aminoquinolines to reduce the relapse rate and destroy gametocytes.

Earlier trials with pyrimethamine in single doses of 25 mg. for controlling a malarial attack were very encouraging (Archibald, 1951 ; Schneider *et al*, 1952 ; Schneider, Montezin and Behen 1952a and 1952b ; Singh *et al*, 1952 and 1953 ; McGregor and Dean Smith, 1953). But within a year after the publication of these successful reports, a number of reports began to appear revealing the inadequacy of single dose treatment with it (Field *et al*, 1952 ; Gilroy, 1952 ; Chaudhuri, 1953 ; Chakravarty and Chaudhuri, 1953 ; Laha, Singhal and Navani, 1953 ; Khatri and Samuels, 1953 ; Srivastava, 1953 ; Srivastava, Chakraborti and Mukherjee, 1953). Suggestions were made to increase the dose from 25 mg. to 50 mg. and to repeat it after 24 hours, but even a dose as high as 300 mg. was not enough to halt an attack of falciparum malaria (Wilson and Edeson, 1953).

Follow-up treatment with suppressive regimes at regular intervals is essential after single dose therapy for prevention of relapses and incidentally re-infection. Weekly doses of proguanil (0·3 g.), or pyrimethamine (25 mg.) or fortnightly 7 chloro-4(3-diethyl aminomethyl-4-hydroxyanilino) quinoline (0·4 g.), chloroquine (0·4 g.) or mepacrine (0·4 g.) have been found effective by us.

Treatment of an acute attack with a minimum and safe dose of a drug in the field is more practicable than the maximum recommended dose and so also the suppressive therapy in fortnightly doses is preferable to daily, bi-weekly or weekly doses. Some workers have gone still further and showed that administration of a single dose of 7 chloro-4 (3-diethylaminomethyl-4-hydroxyanilino) quinoline a month was also effective (Field *et al*, 1952 ; DeSmet, 1954).

Summary

Since 1946 we have tried a number of synthetic drugs in single doses in the treatment of semi-immune malaria patients infected mostly with *P. falciparum* or *P. vivax*. In single dose treatment of malaria best results were obtained with 0·6 g. base of 4 aminoquinolines and mepacrine, in each case the temperature subsiding and the parasites in the blood disappearing in two days in the vast majority of cases. Proguanil (0·3 g.) and pyrimethamine (50-100 mg.) were much lower in action and sometimes ineffective ; these drugs are therefore, not recommended for acute cases of malaria.

The advantage of single dose treatment is obvious in rural dispensary practice where the dose can be given to an illiterate patient and the uncertainty of administration at home is avoided.

Relapses would inevitably occur at different intervals after such treatment but usually not before 3 or more weeks after mepacrine or 4-aminoquinolines ; hence the patient should be advised to take a weekly dose of any of the above drugs after the treatment. This in our experience affords a very high degree of protection against relapses and fresh infection, and remarkably reduces

splenomegaly. In this respect 4-aminoquinolines have proved superior to proguanil and pyrimethamine; indeed 4-aminoquinolines are capable of giving the same amount of protection. Encouraging results have also been obtained recently with fortnightly doses of mepacrine.

It is worth noting that of the potent synthetic antimalarials mepacrine is the cheapest and has obvious economic advantage in treatment of malaria in large communities.

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REFRESHER COURSE

PEPTIC ULCER— DIAGNOSIS AND MANAGEMENT

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Peptic ulcer is one of the commoner disorders the medical practitioner has to deal with. It implies an ulcer caused by the peptic activity of gastric juice, in the regions exposed to its action and according to its anatomical location it is called gastric or duodenal.

DIAGNOSIS

The diagnosis of peptic ulcer is based chiefly on clinical examination, supplemented by laboratory and roentgenological aids. The disease is more commonly met with in males than in females. The age incidence varies from 14 to 72 years. The earlier the age, the greater is the possibility of the ulcer being duodenal.

CLINICAL EXAMINATION

The verbal examination—The verbal examination is more informative than the physical. The most consistent diagnostic feature is its chronicity; the duration may be of several years. The next is the perodicity of ulcer symptoms; this is more common in duodenal ulcer. The presenting complaint in almost all cases is the pain in the epigastrium, in its left half or middle line in gastric and in its right half in duodenal ulcer. The pain is intermittent, appearing after meals—within one hour in gastric and after 2 hours in duodenal. It is temporarily relieved by food or alkalies, more often in duodenal than in gastric ulcer. The character of the pain is described variously, e.g., burning, etc., but is of no diagnostic significance. The pain is a localised one without any radiation.

In some cases acidity, heartburn and regurgitation of acid gastric contents accompany the pain. By themselves they are not characteristic of this disease.

Physical examination—There may be no physical findings. The only sign of any significance is localised tenderness in the epigastrium with or without muscular rigidity. Its presence in the right side of the epigastrium is indicative of a duodenal ulcer.

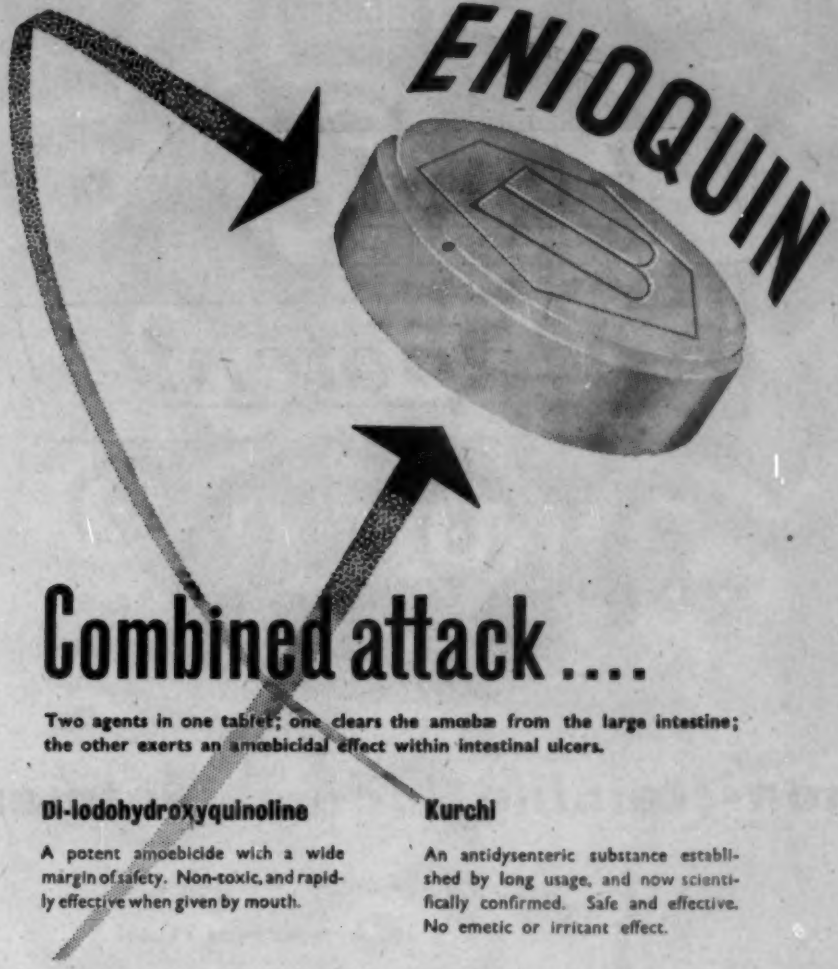
LABORATORY AIDS

Gastric analysis—Gastric analysis is of aid when the quantity of free acid exceeds 80 units (80 c.c. of N_{10}HCl per 100 c.c. of gastric juice) after a test meal—indicating the presence of peptic ulcer, more often duodenal. The absence of free acid needs further investigation before any inference can be drawn.

Examination of stool for occult blood—The presence of occult blood in the stool even after the diet (free from haemoglobin) given for 3 consecutive days is not dependable as it is often difficult to exclude the presence of other sources of bleeding.

ROENTGENOLOGICAL AIDS

The presence of the ulcer crater or niche is the only direct evidence of peptic ulcer. In case of duodenal ulcer the indirect evidence is afforded by a deformed duodenal cap. The absence of these signs does not prove otherwise.



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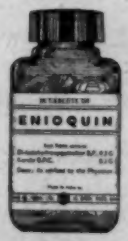

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Differential Diagnosis

A diagnosis has to be made from some diseases simulating peptic ulcer.

Chronic gastritis—The complaint of the patient here is more a discomfort than actual pain. Tenderness when present is over a wider area in the epigastrium.

Carcinoma of the stomach—The duration seldom exceeds 18 months. The pain has no definite relationship with meals but often comes immediately after meals. The appetite is poor. Sometimes coffee-ground vomiting is a feature.

Ulcer-cancer—Occasionally the chronic gastric ulcer may become malignant. The young age of the subject, the high acid in gastric analysis and roentgenological evidence of ulcer on the lesser curvature, the ulcer being less than 2·5 cm. in diameter are points in favour of the ulcer being benign.

Chronic cholecystitis—Here the pain is much less regular in relation to food, tenderness being present over the region of the gall bladder. Cholecystography may help.

Chronic appendicitis—The epigastric pain when present differs from that of a peptic ulcer in having a less regular relationship with meals and is seldom relieved by food or alkalies. The tenderness is generally more marked in the right iliac fossa than in the epigastrium even when there is no spontaneous pain in the former situation. Radiological examination may help.

Chronic intestinal amoebiasis—It sometimes simulates chronic peptic ulcer due to reflex pylorospasm. Epigastric pain when present often bears no definite relationship to meals. Examination of stools, gastric analysis, and radiological investigations, and the results of specific therapy may help.

Hookworm disease—Sometimes there may be pain and tenderness in the epigastric region and even melaena simulating duodenal ulcer. But the pain is much less regular in relation to food. Examination of stools, blood and the result of specific therapy will give a decision. Radiological investigations will help.

Management

Medical Treatment:

The management of an uncomplicated case of chronic peptic ulcer is essentially the same whatever be its position. The object of medical treatment is to relieve the symptoms, heal the ulcer and prevent recurrences.

Initial management. In the initial management, the achievement of relief of pain and promotion of healing of ulcer are aimed at by the adoption of the following measures.

Rest—Treatment should begin with the patient in bed for 4 to 6 weeks. This will control disordered gastric motility and shorten the time of healing. The patient may be allowed to get up every day to have a bath and open his bowels.

Alimentation—There are three important factors: (*i*) feeds are to be taken at fixed intervals starting at 8 o'clock in the morning and usually ending at 10 o'clock at night, (*ii*) the intervals should be short, usually 2 hours, and (*iii*) the diet to begin with should be bland consisting of milk and milk products with one ounce of sugar during the first week or two. The feed should consist of 6 oz. of milk every 2 hours commencing at 8 A.M. and ending at 10 P.M. and after that every 4 hours at 2 A.M. and 6 A.M. if the patient is awake. The calorie value of this diet will approximate between 1100-1300. If fresh milk is not available dried milk or malted milk may be substituted. It is intended to diminish the mechanical effect of rough food and to reduce the quantity of free hydrochloric acid during the time when food and its accompanying secretions are present in the stomach.

Diminution of acidity—The healing of an ulcer is retarded in presence of acid. For neutralisation of free hydrochloric acid administration of alkalies is indicated. The danger of administration of systemic alkalisers as neutralising agents in the treatment of peptic ulcer lies in the induction of alkalosis. The newer antacids aluminium hydroxide and magnesium trisilicate have the great merit of not inducing alkalosis. The dose of either is a teaspoonful in an ounce of water to be given half an hour after each feed with a double dose after the last feed at night at 10 P.M. It need not be given if feeds are given at 2 A.M. and 6 A.M. It is to be remembered that aluminium hydroxide has a constipating effect whereas magnesium trisilicate has a laxative effect. If after administration of aluminium hydroxide for a couple of days it is found to be causing constipation, the best practice would be to start in the morning after the first feed with magnesium trisilicate and repeat it half an hour after each successive feed until the bowels move and then replace it by aluminium hydroxide for the rest of the day.

Calcium carbonate and milk of magnesia may be used in place of aluminium hydroxide and magnesium trisilicate respectively.

Sedation—Nowadays it is being recognised that the ulcer patient is of a certain psychological type, particularly one suffering from duodenal ulcer. The defect has been expressed as one of hypermotility, hyperirritability and hypersensiti-

vity not only of the duodenum but also of the patient himself. Physical and mental rest with relaxation may be achieved by sedatives. Phenobarbitone gr. 1 combined with atropine sulphate gr. 1/100 is given three times a day in a teaspoonful water half an hour before feeds at 7-30 A.M., 1-30 P.M. and 9-30 P.M. The administration of atropine will decrease the volume output of acid, decrease tonic motility and should relieve pain and promote healing.

In those cases where the duration of ulcer-dyspepsia is short, relief of symptoms is expected to be obtained with the above management by the end of the first week. If not the same treatment is to be continued during the second week. In a great majority of subjects a fortnight's treatment is expected to produce satisfactory results in the form of amelioration of symptoms.

In some cases it is observed that pain is relieved but acidity persists which may be troublesome to the patient. In such cases hourly milk-feed 3 oz. at a time with hourly administration of antacid may be given a trial. If this fails to control acidity within a week, continuous intragastric drip of milk at the rate of 10 to 15 drops per minute together with antacids every 2 hours by mouth may be given ; this is expected to relieve symptoms within four days.

When complete relief of symptoms have been achieved the diet is to be increased. For the first two days 2 oz. of bread and 1 oz. of butter are added to the first feed. For the second two days cooked soft rice 2 oz., mashed potato 2 oz. are added to the 12 o'clock feed. For the next 2 days 2 oz. bread and 1 oz. butter are added to 4 P.M. feed. For the last 2 days of the week soft rice 2 oz., mashed potato 2 oz. are added to the 8 P.M. feed. At the end of this week the calorie value of this diet will approximate 2000.

Antacids and sedatives are to be continued as before.

In the following week the patient is allowed to take feeds as below :

8 A.M. —Bread 2 oz., butter 1 oz., egg 1, milk 6 oz.

10 A.M. —Milk or milk substitutes 6 oz.

12 Noon—Soft rice gradually increased to 4 oz., butter 1 oz., boiled mashed vegetables, e.g., potato, green banana or both, one to two table spoonfuls, green vegetables, e.g., unripe papaya, white pumpkin made into curry (without chillies or black pepper)—one to two tablespoonfuls. Boiled fish 2 oz. increased to 4 oz., milk 4 oz.

3 P.M. —Milk or milk substitutes 6 oz.

5 P.M. —Same as at 8 A.M.

7 P.M. —Milk or milk substitutes 6 oz.

9 P.M. —As at noon.

Fish can be replaced by chicken, or meat 2 to 4 oz. Egg may be taken soft boiled or poached.

The calorie value of the above diet will be near about 2500 calories.

For those who are vegetarians 'channa' (casein) can be recommended as a substitute for eggs, fish or meat. Two oz. of channa is equivalent to one egg, 1 oz. fish or meat approximately, from the standpoint of nutrition. Channa can be served in the form of plain channa with sugar, or sweet preparations, or fried channa made into curries or dessert of channa.

The antacid in the dosage advocated above is to be given half an hour after the 8 A.M., 12 noon, 5 P.M. and 9 P.M. feeds with double the dose after the last feed.

Phenobarbitone and atropine sulph in the dosage recommended before are to be given half an hour before the two principal meals.

During the course of above treatment one multivitamin tablet (with minerals) twice a day is to be given in order to make up vitamin deficiencies.

AFTER-TREATMENT. A great majority of ulcers treated medically will heal within 6 weeks. Any patient who fails to show a response to treatment within two to three weeks should be most carefully reviewed to exclude complications or associated diseases. After the healing period is over the main problem is that of recurrence and to prevent recurrence the patient is allowed up by increasing stages and progresses to a post-ulcer regime of diet and habits which the patient is instructed to follow for a minimum period of two years or if possible permanently after 6 weeks of above treatment.

Diet—The time interval between the small feeds should not exceed 2 hours and that after principal meals 3 hours. Small feeds should consist of at least 6 oz. of milk or bread 2 oz., butter 1 oz. and egg 1. Meals should consist of soft rice, bread, boiled and mashed potato, vegetable curries prepared from those vegetables which are soft and free from fibres and seeds (potato, sweet potato, green banana, green papaya, white pumpkin, carrots beet), fish, egg, meat (should not be tough) and milk preparations.

Fried food in all forms is forbidden.

Extra salt, pepper red or black, acid tasting substances, e.g., lemon, tamarind, 'dahi', chutneys and gritty substances, e.g., nuts are to be avoided.

Habits—Food should be properly chewed and should not be hurried through. Rest for 15 to 30 minutes after the principal meals is essential.

Strong tea, coffee, alcohol, smoking and taking tobacco in any form are to be avoided.

Drugs—Antacid should be taken an hour after two principal meals, before retiring at night and also when the slightest acidity, heartburn or epigastric discomfort is felt.

Attention should be paid to the teeth. The patient should lead a regular life and should consult his physician with the least possible delay on return of any symptoms.

SURGICAL TREATMENT :

Although the treatment of a case of chronic peptic ulcer is essentially medical, sometimes the question of surgical treatment will arise. The indications for surgery are as follows :

(1) Failure of medical treatment. History of repeated relapses despite an efficient medical treatment. It occurs more commonly with an intractable duodenal ulcer.
(2) Recurrent haemorrhage. While the immediate treatment of ulcer-haemorrhage in most cases is medical, recurrent haemorrhages should be treated by surgery.
(3) Suspected malignancy. The failure of gastric ulcer to respond to medical measures within a few weeks at the most indicates the advisability of exploration to confirm or disprove the suspected malignancy.
(4) Organic obstruction.
(5) Perforation.

TREATMENT OF CHOLERA

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Prompt and correct management of a case of cholera assumes added importance owing to the explosive nature of the disease. Attention directed towards the management of a single case is not enough. Every practitioner has a duty to see that the case under his care may not serve as a source of infection to others in the household or locality.

The incidence and mortality amongst the inoculated are much less. 2 injections of vaccine (8000 millions per c.c.), ½ c.c. followed at a week's interval by 1 c.c. are recommended. In times of urgency a single injection of 1 c.c. affords considerable protection. Dilute acids (acid hydrochlor dil (B.P.) ½ dr. in a tumbler of water) taken through a straw has been recommended. The possible role of the newer antibiotics (specially terramycin) which have rapid vibriocidal action *in vitro*, in prevention has been suggested, but their scope has not been fully explored and their value remains to be proved.

The curative treatment depends upon an appreciation of the changes brought about in the human system by cholera.

Copious diarrhoea and vomiting during the stage of evacuation rapidly leads to dehydration. This leads to a diminution of extracellular fluids involving both the circulating plasma volume and the interstitial fluids. The latter continuously parts with water and salts to replenish that which is lost from the vascular compartment. As fluid loss continues there is a diminution of circulating blood volume accompanied by haemoconcentration. Disproportion between the vascular capacity and its contents occurs with the development of peripheral circulatory failure. This is the stage at which a medical practitioner is usually asked to see the case.

At this stage the immediate objectives are :

1. To restore the water and electrolytes lost from the body and thus treat both dehydration and peripheral circulatory failure.

2. To anticipate, minimise or correct the effects of biochemical imbalance of body fluids including acidosis and uraemia. Normally the lungs and the kidneys are the guardians of the mechanism ensuring constancy of the composition of body fluids. The possibilities of such imbalances occurring in cholera are enhanced by continued anuria : with the exception of CO_2, practically the only channel of excretion of all other ions are the kidneys.

3. To treat complications.

To achieve these objectives, infusions of fluids are necessary. The main components of the common restorative fluids are :

1. Water ;
2. NaCl solutions ;
3. $NaHCO_3$ solutions or 1/6 molar Na lactate solutions ;
4. Glucose solutions ;
5. Plasma (or plasma substitutes) in rare instances.

Occasionally other ions such as $CaCl_2$ or KCl are added to the fluids ; the former during initial transfusion, the latter only in places where adequate biochemical control is possible. KCl is not used during the initial transfusions but only later, if and when there are indications of hypopotassaemia.

Infusions of intravenous fluids are usually of the following types:

1. Hypertonic saline:
   NaCl ... gr. 120
   $CaCl_2$ ... gr. 4
   Aqua destillata ad O1
2. Normal saline:
   NaCl ... gr. 90
   Aqua destillata ad O1
3. Alkaline saline:
   NaCl ... gr. 90
   $NaHCO_3$ gr. 180
   Aqua destillata ad O1
4. Hypotonic alkaline saline:
   NaCl ... gr. 60
   $NaHCO_3$ gr. 180
   Aqua destillata ad O1
5. 5 per cent $NaHCO_3$ solution or 1/6 molar Na lactate.
6. 5 per cent, 10 per cent and 25 per cent glucose solutions.

Indications of Parenteral Fluid Administration

1. *Clinical features of dehydration.*

Thirst, hoarseness or feebleness of voice, dry tongue, anuria, low eyeball tension, sunken eyeballs and cheek, inelastic skin, wrinkling of the skin of the fingers (incidentally this enables a rough estimate of the magnitude of interstitial fluid depletion to be made), cramps, poor volume and tension of the pulse and low blood pressure (below 75 mm. of Hg. systolic in adults).

2. *High specific gravity* of the blood (normal 1054 in Indians).

Specific gravity over 1060 indicates the imperative necessity of parenteral fluids.

Details with regard to the Administration of Fluids

Route of administration.

Fluid should be administered by the intravenous route unless there are definite contraindications, such as a rectal temperature above 103°F, in very small children or in cases in whom the veins are not available recourse may be had to the subcutaneous route. This route is not satisfactory and should be considered only as second best.

Quantity of fluid:

An adult, with signs of well marked dehydration needs 3 pints of fluid during the initial transfusion, and this quantity should be administered in such cases even when estimation of specific quantity is not possible. It has been accepted that each point in the rise of specific gravity above 1060 necessitates one pint of fluid. Thus a patient with the specific gravity of blood of 1061 needs one pint, 1062 two pints, 1063, 3 pints. Not more than 3 pints should be given by the continuous method during a single transfusion. Drip saline at the rate of 60 to 120 drops per minute should be continued after the initial three pints if, (*a*) the initial specific gravity of the blood was more than 1065; (*b*) if signs of dehydration are not relieved; (*c*) if copious evacuations continue during the transfusion. During this period the rate of saline transfusion may be increased if copious evacuation brings about a recurrence of signs of dehydration or fall of blood pressure.

Type of Saline:

For the initial transfusion two parts of hypertonic saline and one part of alkaline saline are given by the continuous method and subsequently hypertonic saline continued by the drip method if necessary. The two should not be mixed.

For subsequent transfusions during the first 24 hours of treatment, the proportion of the requisite quantities is 1 part of hypertonic saline and 2 parts of alkaline saline. The theoretical objection that hypothetical toxins may be drawn into the circulation by the hypertonic nature of the infusate, appears invalid.

Even when the initial salt depletion is made up, there is the possibility of acidosis and uraemia setting in, if anuria is persistent. To anticipate these eventualities, Rogers recommended administration of alkalies from the commencement of treatment. The wisdom of this practice has been fully borne out by the passage of years. In addition we have found that large quantities of bases ($NaHCO_3$) are passed in the stools and it stands to reason that this should be replaced. In the face of anuria or oliguria, and after the initial salt depletion has been made up, the recommendation of hypotonic saline with alkalies appears sound in practice. If transfusions are required 24 hours after the commencement of treatment, hypotonic saline with alkali is usually administered.

No hard and fast rules can be laid down for further administration of fluids but some guiding principles are suggested under the heading of treatment of complications.

Administration of 100 c.c. of 25 per cent glucose after the initial saline transfusion, repeated at 4 to 6 hourly intervals throughout the course of treatment is desirable.

The advantages of administering hypertonic saline in the initial stages are many. Salt depletion is quickly replenished and the restoration of

circulating blood volume is maintained for a much longer period. Transudation of fluids into the intestinal lumen is minimised and evacuations are lessened. Cramps are abolished after the first few ounces.

Rate of administration:

The usual rate of administration is 5 minutes for the first pint, 10 minutes for the second pint and 15 minutes for the third pint. If continued administration beyond this is needed, at the initial transfusion this should be by drip at the rate of 60 to 120 drops per minute. This is only a general rule, and each case has to be individualised according to the way he responds and reacts.

Not more than 3 pints at the initial and 2 pints for the subsequent transfusions should be given by the continuous method.

Temperature of fluids:

If the rectal temperature is 101°F or above it is usual to give the saline at room temperature in the tropics. If it is below 97°F. the saline should be warmed to body temperature (checked roughly by pouring the saline on the back of the hand). Further refinements have been suggested but these are not possible in ordinary practice.

Subcutaneous Saline:

It is not desirable to give saline intravenously if the rectal temperature is above 103°F. Even when it is above 101°F. it should be given slowly and with caution. Hyperpyrexial reactions are particularly likely to occur under these circumstances. It is also not possible sometimes to administer the saline intravenously to small children. When subcutaneous saline has to be given it is desirable to add 1 c.c. of Hyalase or similar preparation to each pint. This facilitates rapid absorption and is of great value. Alkaline saline should not be given subcutaneously or intramuscularly as this will lead to sloughing. Hypertonic saline should also not be given subcutaneously.

Adverse effects of saline and indication for stopping intravenous saline.

The possibilities of pyrexial reaction, circulatory overload, respiratory distress, cerebral oedema and air embolism should be remembered during administration. The following clinical manifestations would indicate slowing or stoppage of administration.

(1) Precordial distress—oppression or pain. (2) Headache. (3) Cough. (4) Dyspnoea. (5) The pulse usually slows down when saline is being administered. If the rate starts rising during administration, after the initial slowing, this is a very valuable and early indication for reducing the rate of flow, or for stopping the administration. (6) The appearance of congested veins in the neck. (7) Occurrence of chill and rigor and rise of temperature.

Sometimes it is possible to commence administration of the saline after these adverse effects have passed off. On other occasions it becomes necessary to abandon intravenous administration and have recourse to the subcutaneous route.

Indications for repetition of transfusions:

Copious evacuations resulting in recurrence of signs of dehydration (enumerated), fall of blood pressure with rise of specific gravity of the blood above 1060 indicate readministration of appropriate saline.

Administration of saline to children:

The adverse effects of dehydration occur very rapidly in children and infants. Their kidneys are also unable to deal with electrolyte imbalance in the same way as adults. The treatment of fluid depletion in children is notoriously difficult. The high mortality of cholera in children is due to these factors. It is therefore difficult to generalise on the principles to be followed.

The following plan is suggested.

Initial transfusion—

Quantity—1 oz. per kg.

Rate—not faster than 1 oz. in 2 minutes for the first 5 ounces. Subsequently slower if necessary.

Type—5 per cent glucose in normal saline —2 parts. 1 per cent sodii bicarbonate in hypotonic saline—1 part.

Subsequent transfusion—⅓ normal saline with 5 per cent glucose.

Points for caution:

Alkaline saline cannot be sterilised by boiling. Part of the sodium bicarbonate is converted to toxic carbonate by this process. Requisite quantities of $NaHCO_3$ powder from autoclaved packets are added to the appropriate saline or sterilised ampoules are used instead.

Diet:

In the initial stages only water, glucose water (2 oz. to 1 pint) and salted barley water may be given. As the condition improves, whey (ghole), strained parched rice gruel are added before gradually resuming normal diet.

It is not advisable to give fruit juices or protein-containing food as long as anuria persists.

Specific drugs:

Both the sulpha group of drugs and antibiotics have failed to influence the clinical course of cholera. The former may even be harmful in the stage of anuria and should not be given.

If at all it is decided to give any antibiotics owing to their vibriocidal action, oxytetracycline intravenously is probably the most suitable as it appears in the bowel lumen very rapidly if given by this route.

There is no clear evidence that phage is of value. Only moderate doses of kaolin (1 oz. to 1 pint of water) is recommended as a drink. The administration of permanganate pills or essential oil mixture is not recommended.

Treatment of complications:

1. Recurrent collapse.

After body fluid depletion is restored by transfusions, continued evacuations may lead to reappearance of peripheral failure. The cycle may be repeated more than once. The essential diagnostic features of such a state are a rise of the specific gravity of blood (indicating dehydration) with a fall in blood pressure and imperceptibility of pulse. The indications are for intravenous transfusion of saline.

There is however another variety in which the specific gravity of the blood is normal or low and the patient suffers from recurrent collapse. Administration of saline sustains the pulse only for transient periods, and the patient drifts into collapse without sufficient evacuations to account for the state. The low specific gravity indicates that dehydration has been corrected. The state is due to pooling of blood in the capillaries. It is likely that the initial peripheral failure cut off the nutrient flow to the tissues so markedly that due to anoxia and accumulation of metabolites the functions of the capillary system was interfered with. It is obvious that continued administration of saline is not indicated in such cases, as this will only lead to collection of fluid in the interstitial spaces. Plasma or its substitutes (1 pint), cortical hormones, strychnine gr. 1/16 hypodermically are indicated. The place of vasoconstrictors in such cases is debatable. Recently however Nor. adrenaline with I.V. transfusions have been used in peripheral failure.

The treatment of recurrent collapse may be summarised as follows:

1. With high sp. gr. of blood (dehydration not corrected or continued losses in excreta)—repeat transfusions.

2. With low sp. gr. of blood (dehydration corrected)—No further indication of saline, plasma or plasma substitutes, cortical hormones, strychnine, vasoconstrictors.

2. Uraemia and Acidosis.

The nature of uraemia in cholera is extrarenal. The oligaemic peripheral circulatory failure leads to renal anoxia and anuria. The clinical syndrome of uraemia develops if anuria is prolonged. Rapid accumulation of degradation products of nitrogeneous metabolism (such as urea, N.P.N., phosphates and potassium) occurs in the blood because the only channels of effective elimination of these substances are the kidneys. The uraemic state is often complicated by acidosis. The latter is initiated by loss of bases ($NaHCO_3$) in the stools and aggravated by retention of acid metabolites which cannot be excreted by the kidneys.

New views on the management of such states have been formulated by Bull *et al* and there is no doubt that treatment on these lines adapted to cholera will soon find its place as a valuable addition to our therapeutic resources.

Till then the following plan is recommended:

1. Uraemia with low B.P. and high specific gravity of blood.

Dehydration has to be corrected in such case. Glucose 5 or 10 per cent solution in adequate quantities are indicated. Alkalies may be given cautiously (5 per cent sodii bicarb—½ pint) if sufficient alkalies have not been administered previously or if acidosis is manifest. ½ normal saline may be added to 5 per cent glucose if there is clinical evidence that salt depletion has not been made up.

2. Uraemia with normal or high B.P.

There is no indication in such states to pursue administration of electrolytes. The patient should be given glucose orally and 10 per cent glucose solutions intravenously. Total fluids administered should balance obligatory losses through the skin and lungs (usually about 1000 c.c. each 24 hours) in addition to those lost in the evacuations. The latter should be replaced quantitatively by half-normal saline. The ideal suggested by Bull *et al* is to give 400 g. of glucose each 24 hours. This is however impracticable in many cases of cholera and one has to compromise by giving 750 to 1000 c.c. of 10 per cent glucose by I.V. drip (75 to 100 g. glucose) in addition to whatever amount is taken by mouth. All fluids must be free from electrolytes. In the state of anuria no fruit juices or any other fluids except glucose solutions are desirable. The treatment of the uraemic state in cholera cannot be planned rationally without at least the estimation of B.P. and specific gravity. Heat to the loins and penicillin to combat secondary infections are recommended.

3. Hyperpyrexia.

Pyrogen-free distilled water should be used for preparing all solutions for intravenous injections to minimise the risk of this complication. Iced sponging and sheeting, ice cap and iced rectal saline may help to tide the patient over during this critical stage. Paraldehyde—7½ c.c. I.M. may be used to combat the accompanying restlessness and delirium.

4. Hiccough and Vomiting.

A powder such as the following is useful:

Chloretone—gr. iv.
Phenobarbitone sodium—gr. ½.
Atropine sulph.—gr. 1/200.
Ft Pulv one.

May be repeated every ½ hour for 4 doses.

Other measures such as CO_2 inhalations (6 per cent in O_2) and mustard plaster over epigastrium may be tried for hiccough. Atropine sulphate—gr 1/100 with sedatives like phenobarbitone sodium gr. 1½ I.M. may be effective for vomiting.

5. Tympanitis.

Hot fomentations to the abdomen, subcutaneous injection of pitressin 5 units, or prostigmine one ampoule I.M. usually helps.

6. Miscellaneous complications.

Pregnant women almost invariably abort during the course of cholera and arrangements should be ready for this emergency.

Watch must be vigilant for inflammatory complications such as parotitis and pneumonia, local sepsis or thrombophlebitis of veins. There may be gangrenous sequelae of the scrotum and penis or sloughing of the cornea. Most of these are treated by local measures and injections of penicillin.

Cerebral and coronary thrombosis occasionally occur during the course of, or convalescence from cholera. Watch must be kept for these as well.

Cholecystitis and hypoproteinaemia and oedema occur during the convalescent phase and should be dealt with adequately.

The convalescent phase of so serious a disease is surprisingly rapid and it is not uncommon to see patients walking out of hospital on the 7th day after admission feeling perfectly fit.

The principles on which the present treatment of cholera are based, were formulated by Sir Leonard Rogers in the early part of this century. He reduced the mortality rate of this disease from 60 per cent to the neighbourhood of 20 per cent and we owe a deep debt of gratitude to him for his untiring devotion to the study of this disease. Rapid strides are being made in our knowledge of the distribution and composition of the body fluids and their changes in disease. There is no doubt that these will soon have more extensive application to the problems of treatment in cholera, and fatality from this disease will be further reduced.

PRACTITIONERS' SERIES

CHEMOTHERAPY IN PULMONARY TUBERCULOSIS

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Chemotherapy is an essential part in the treatment of pulmonary tuberculosis. This has been possible because of the discovery of more than one strong antibacterial drug against *M. tuberculosis*. Of the many such drugs only three have been found to be suitable for general use because of their comparative freedom from toxic and side effects in clinically effective doses. These three drugs are streptomycin, para-aminosalicylic acid (P.A.S.), and isonicotinic acid hydrazide (isoniazid). Of these drugs streptomycin and isoniazid are almost of equal antibacterial effect against *M. tuberculosis* and P.A.S. somewhat less effective. Used individually, all these drugs have the greatest disadvantage of being effective for a short period only, the bacteria developing a light degree of resistance against the drugs. For this reason, in the early stages of their use it was thought necessary to restrict their application only in cases of the fatal types of tuberculosis like miliary or meningeal tuberculosis and to the acutely progressive types of pulmonary tuberculosis which were not controllable by other available methods of treatment. Subsequently however when it was found that when two antibacterial drugs were used in combination in suitable doses, development of drugs resistance was reduced to a negligible minimum. Since then the scope of chemotherapy has been widely extended. It was also found that when used in combination these drugs can be effective in such low doses that it was possible to continue their use over sufficiently prolonged period until the disease was completely controlled, without the risk of any serious toxic complications. With these two major drawbacks eliminated, the extensive and prolonged use of chemotherapy in all types of pulmonary tuberculosis has proved its worth.

In almost every country a remarkable fall in the mortality rate from tuberculosis has been noticed since about 1947 when the antibacterial

drugs came into extensive use in all forms of tuberculosis. A parallel fall in the morbidity rate has not been seen, indicating that the fall in mortality is not entirely due to efficient preventive measures. This success has been achieved partly by the direct effect of chemotherapy in the control of many cases of tuberculosis and partly by rendering the practice of major chest surgery safe in many cases of pulmonary tuberculosis which are not controlled by medical measures alone. Apart from reduction in post-operative tuberculous complications, more patients are how rendered suitable for thoracoplasty and resection by chemotherapy.

There is thus little doubt that modern antibacterial drugs are mighty weapon against tuberculosis. But because of the disadvantage of development of drug resistance, there is a great danger of those weapons being lost to us unless the drugs are used properly. The problems of drug resistance has not yet been finally solved. But as a result of some strictly controlled trials on scientific lines with different combinations of these antituberculous drugs certain facts regarding the prevention of drug resistance have been established, and principles for the use of these drugs have been laid down.

In acute cases of pulmonary tuberculosis, if the drugs are used alone drug resistance develops in the following rate after 3 months' treatment.

Streptomycin—70 per cent, P. A. S.—24 per cent and Isoniazid—69 per cent.

In M.R.C. trial resistance to isoniazid was 11 per cent at the end of first month, 52 per cent at the end of second month and 71 per cent at the end of third month.

It was also found that drug resistance developed more frequently in the acutely ill patients with extensive caseous or cavernous disease than in less ill patients with limited pneumonic or scattered foci. Resistance to streptomycin develops less often when it is given intermittently twice a week.

When the drugs were used in combination the incidence of drug resistance was found to be remarkably low and the clinical results were better. Three combinations have been used in these trials, namely streptomycin with P.A.S., streptomycin with isoniazid, and P.A.S. with isoniazid. Streptomycin has been used in doses of 1 g. daily, on alternate days or biweekly, P.A.S. has been used as sodium salt in doses of 20 g., 10 g. or 5 g. a day, and isoniazid has been used in doses of 200 mg. a day. On an analysis of the results of these trials it has been found that clinical results obtained in these three combinations with different doses were more or less similar in identical cases, except with streptomycin and isoniazid, when the results appeared to be somewhat better. In respect to development of drug resistance however, the results depended more on the doses.

Indications of chemotherapy—The committee on chemotherapy of the American College of Chest Physicians reported in 1953 that in the U.S.A. chemotherapy had been accepted as a routine treatment in all cases of active and potentially progressive tuberculosis along with other measures such as sanatorium treatment and rest etc. This however does not exclude collapse therapy when indicated. It has now been generally accepted that when the diagnosis is made, all cases of tuberculosis should have an initial course of chemotherapy along with bed rest and other hygienic measures.

Duration of treatment—As stated above, with proper combinations, these drugs can now be used over longer periods without danger of drug resistance or serious toxic symptoms. There is thus now a tendency to use them for 6-8 months or longer. Some prefer to use them until the disease is completely arrested and then for another 2 months. During this treatment however, collapse or surgical treatment should be done if indicated, specially in those cases where the sputum remains positive after the 3rd month. Continuation of treatment with the antibacterial drugs after this has been seen to cause more drug resistance.

Failure of treatment—The main causes of failure of chemotherapy alone are (1) Drug resistance, (2) toxic symptoms or sensitisation to the drugs, (3) persistent cavities, not healing due to mechanical factors, (4) large encapsulated caseous areas, (5) bronchial stenosis for healed endobronchial disease.

Drug resistance and toxic symptoms may be avoided by proper dosage of the drugs. Sensitisation is obscure and difficult to anticipate or prevent. The other eventualities should be treated with appropriate collapse and surgical means. It is necessary to assess at an early stage of treatment the likelihood of a given lesion to resolve or heal completely on chemotherapy alone or to require surgery and to plan the treatment accordingly. In any case a regular check up on the progress of the patient by repeated x'ray and sputum examination should be kept. If the lesions show progressive resolution or healing and the sputum remains negative after the 3rd month, chemotherapy should be continued until no signs of activity are present and then for another two months.

Choice of drugs—It is generally agreed that streptomycin and isoniazid should not be used together in the first instance except in very acute and desperate cases, like miliary or meningeal tuberculosis, because if resistance to one of the drug develop and is not detected in time by proper

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sensitivity tests, the bacilli develop resistance to the other drug rapidly. Thus both the strong antibacterial drugs would be lost to the patient.

It is therefore desirable to use always either streptomycin and P.A.S. or Isoniazid and P.A.S. The latter has the advantage of being both administrable orally. Thus patients living long distances away from available doctors are better treated with isoniazid and P.A.S. In elderly people, streptomycin has a greater tendency to cause 8th nerve disturbances, and so in old people also isoniazid and P.A.S. would be preferable. Similarly in children, who resent repeated injections, this combination is very useful. Streptomycin, on the other hand, has the advantage of requiring frequent visit by the doctor, and therefore, better supervision can be ensured.

Sometimes P.A.S. cannot be given in adequate doses because of gastrointestinal disturbances. In such cases it is better to give streptomycin and isoniazid rather than use smaller doses of P.A.S. P.A.S. in enteric coated tablets or granules is better tolerated. But with these preparations it is always better to use a higher dose as absorption may be uncertain.

Toxic symptoms—Streptomycin and dihydrostreptomycin have got a toxic action on the 8th nerve. Streptomycin causes more vertigo and dihydrostreptomycin causes more deafness; when given as 1 g. 3 times or twice a week, the toxic symptoms are very much less. The toxicity on the 8th nerve may still further be reduced by using a combination of streptomycin and dihydrostreptomycin in equal parts. Other toxic symptoms like damage to the kidney or encephalopathy are rare. Streptomycin should be used with caution in the presence of damaged kidneys.

Apart from local gastrointestinal disturbances, P.A.S. has very few toxic symptoms on prolonged use.

Isoniazid may produce mild gastrointestinal disturbances and constipation. Other toxic symptoms are insomnia irritability, hyperreflexia and psychotic states. The latter is sometimes very serious in susceptible individuals. Isoniazid should be used with caution in the mentally unstable patients. Lately cases of neuritis have been reported as complication of isoniazid therapy.

Hypersensitive reactions may occur with all the three drugs. Skin rashes, urticaria, drug fever, purpura, asthmatic attacks and rarely exfoliative dermatitis may be seen. When hypersensitivity develops it may be necessary to discontinue the drug concerned, unless densensitisation can be done. Antihistamine drugs may be tried. But they have not been very successful in preventing sensitivity reactions.

Dosage—Streptomycin sulphate or dihydrostreptomycin sulphate or a combination of both in equal amounts should be given in 1 g. dose by single intramuscular injection. When used with P.A.S., it may be given either daily or on alternate days or biweekly, depending on the acuteness or otherwise of the disease. With isoniazid, however, it should preferably be given daily, or at least on alternate days, but not biweekly.

P.A.S.—Given with streptomycin or isoniazid, the dosage should be between 10 to 20 g. a day, as sodium P.A.S. or its equivalent in paraaminosalicylic acid or its calcium salt.

In patients with lower body weight, below 100 lb., a somewhat lower dosage may be used if higher doses are not tolerated. However in all acutely ill patients, or patients with extensive caseous disease it is always safe to use the highest possible dose.

Isoniazid—It is generally agreed that 3 to 5 mg. per kilo body weight is the proper dose. As toxic symptoms or symptoms of intolerance are rare with isoniazid, it is always better to use a minimum of 200 mg. a day in two divided doses.

Supervision of tuberculosis patients must continue treatment sufficiently long without interruption and in proper dosage. It is difficult to convince patients the need for continuing heavy doses of costly drugs once they are free from symptoms and they readily reduce the dose voluntarily, specially with P.A.S., which unlike many medicines has a very large daily dose to which people are not accustomed, and which is likely to cause some abdominal discomfort. Unless the doctors are vigilant voluntary reduction of doses may baffle the need for combined treatment and drug resistance on large scale may develop.

CASE NOTES

ACUTE ANURIA WITH VOMITING AND HAEMATEMESIS DUE TO SNAKE BITE POISONING

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AND

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The present trend in the treatment of acute anuria favours a conservative line meant to secure optimum

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rest for the injured kidneys and uses a fluid diet with glucose and fat without any protein and electrolytes to tide over the stage of anuria. Under favourable circumstances such a regime is rewarded by the onset of spontaneous diuresis, when the kidneys recover from the injury. Judicious adoption of conservative regime as advocated by Bull *et al* (1949) hardly necessitates other active measures.

In a case of complete renal failure resulting from viper bite, the usual plan to institute Bull's treatment orally could not be executed due to repeated attacks of coffee ground vomiting, haematemesis and associated extreme restlessness. So, the case was treated with large amounts of intravenous glucose with sodi bicarb, calcium gluconate, vitamin C and vitamin K, with gratifying result. The purpose of the present communication is to report the case with special reference to the good response obtained with the intravenous therapy where the institution of Bull's treatment per oral route was out of question.

Case Report

A male patient, K.C.M., aged 45 years, while working in a jungle, was bitten on 13-9-1953 in his right foot by a viper (*Chandra Bora*?). 2 hours after the bite, bleeding started from the gums and right ear. 3 hours later, he was admitted with pain over the right foot, pain in the epigastrium and renal angles and bleeding from the gums and right ear.

On examination, the puncture marks of snake bite were seen in front of the lateral malleolus of the right foot. Pulse was 85/min. and B.P. was 105/85 mm. of Hg. No other abnormality was detected elsewhere. Polyvalent antivenin serum 80 c.c. was immediately given I.V. followed by vitamins C, K and penicillin I.M. The patient was given a light diet for the 1st 3 days after which bread and eggs were omitted from the diet.

For the first 5 days (13-9-1953—17-9-1953), the patient was having pain in the epigastrium and renal angles with bleeding from the gums. He was having vomiting at times which was often coffee-ground in colour and the urinary output gradually decreased. From the 6th day (18-9-1953) onwards, the general condition of the patient quickly deteriorated (*vide* Table 1). There was vomiting, haematemesis and extreme restlessness. The patient gradually passed into a semicomatose condition and was delirious at times. B.P. 160/105 mm. of Hg. Blood biochemical studies showed raised urea (160·0 mg.), N.P.N. (92·0 mg.) and potassium (34·7 mg.). Urine was scanty and contained albumin, R.B.C. and pus cells.

The oliguria subsequently culminated in absolute anuria on the 8th day (20-9-1953) when the amount of vomitus became more than the fluid intake by mouth.

Association of frequent vomiting, haematemesis and extreme restlessness precluded the use of any form of oral therapy. Accordingly the following substances were administered daily from the 9th day (21-9-1953) by the continuous intravenous drip method: (1) 50 per cent Glucose—1000 ml. (2) 10 per cent Sodi bicarb—80 ml. (3) 10 per cent Calcium gluconate—40 ml. (4) Aqueous solution of Vitamin C—1000 mg. (5) Aqueous solution of Vitamin K—20 mg.

Subsequent course—The absolute anuria persisted for 3 days from 8th to 10th day (20-9-53—22-9-1953); the patient remained semi-comatose, was delirious and restless at times. On the 11th day (23-9-1953), the urinary bladder was found to be partially full, and 24 oz. of smoky urine was catheterized. To maintain the fluid balance of the body, 24 oz. of pyrogen free redistilled water was added to the intravenous fluid. Gradually the urinary output increased and the colour became progressively clear. The volume of urine was measured daily and an equal volume of pyrogen free redistilled water was added to the intravenous fluid. This regime was continued for 6 days (21-9-1953—26-9-1953) till full diuresis started with subsequent recovery. During the period of convalescence, the patient was extremely weak, asthenic and even non-responsive which might be due to hypokalaemia as a result of excessive diuresis. The blood potassium was not done at this stage. But the electrocardiogram taken on 30-9-1953 during the stage of convalescence was suggestive of hypokalaemia as evident from the wide QT interval, low and wide T wave (Fig. 2, *vide* Plate).

The clinical, blood biochemical and important urinary findings before, during and after I.V. therapy are shown in Table 1 and Fig. 1.

The E.C.G. (Fig. 3, *vide* Plate) shows the changes suggestive of hyperkalaemia during the stage of anuria as evident from low P wave, wide QT interval, and tall T waves.

Discussion

Treatment on the lines of Bull (1949) was impossible as the patient was vomiting repeatedly with occasional haematemesis—where gastric intubation was out of question. Institution of Bull's treatment by gastric intubation was found to be impossible in anuric cases of cholera where the patients could not retain it (Chakraborty and Chandhuri, 1954). Intravenous preparation of fat, if available, would have been ideal.

When the problem was to replenish the obligatory fluid loss by skin, lungs and faeces and to supply sufficient calories for the essential needs of the vital organs of the body during the stage of anuria, we had no other alternative but to adopt the I.V. route for the administration of restricted amounts of fluid, glucose and other

TABLE 1—CLINICAL FINDINGS

Date	General condition	Epigastric & Renal pain	Gum Bleeding	Vomiting		B.P. in mm/Hg.		Fluid intake	Urinary output
				Nature	Amount	Morning	Evening		
18-9-53 ...	Restlessness+	+	+	Coffee ground	20 ozs.	100/80	110/90	Orally .. 33 ozs. I.V. .. 25% glucose 200 c.c.	14 ozs. urine on catheterisation.
19-9-53 ...	Drowsiness + and at times very restless.	++	+	Coffee ground	38 ozs.	140/105	120/95	Orally .. 39 ozs. I.V. .. 25% glucose 400 c.c.	8 ozs. of urine on catheterisation Haematuria +
20-9-53 ...	Low, drowsiness + & at times very restless.	+++	Slight	Coffee ground & frank haematemesis+	43 ozs.	130/95	130/92	Orally .. 34 ozs. I.V. .. 25% glucose 400 c.c.	0
21-9-53 I.V. therapy started.	Low, drowsy, at times very restless, boisterous and unresponsive.	++	0	Coffee ground & frank haematemesis+	22 ozs.	160/105	140/100	Oral fluid stopped and I.V. therapy started.	0
22-9-53 ...	Low, drowsy, at times very restless, boisterous and unresponsive.	++	0	Coffee ground & slight haematemesis.	10 ozs.	155/100	145/100	do.	0
23-9-53 ...	Low, drowsy, very restless at times boisterous.	+	0	Coffee ground.	10 ozs.	140/95	140/100	do.	24 ozs. of smoky urine on catheterisation.
24-9-53 ...	Low, drowsy, restless at times.	Slight	0	Coffee ground.	12 ozs.	140/90	140/96	do. +24 ozs. of Pyrogen free redistilled water.	38 ozs. of urine on catheterisation more clear than on previous day.
25-9-53 ...	Low, less drowsy and restless at times.	0	0	Bilious.	6 ozs.	90/70	110/75	do. +38 ozs. of Pyrogen free redistilled water.	34 ozs. of urine which could be measured & some urine soiled the bed clothes.
26-9-53 ...	Weaker. Slightly drowsy. No restlessness.	0	0	Bilious.	4 ozs.	130/90	120/85	do. +34 ozs. of Pyrogen free redistilled water.	84 ozs. of urine.
27-9-53 I.V. therapy omitted.	Weak.	0	0	0	0	120/80	115/82	Nasal drip started as the vomiting has stopped. Total amount 134 ozs. given. This consisted of fluid, milk and glucose.	80 ozs. of urine.

From 28-9-53 till discharge from the hospital, patient gradually improved. His urinary output which was too much after the end of anuric phase came to normal gradually. When his appetite became fair and the chance of vomiting was absent—nasal drip was developed and the patient could take his meals. His phlebothrombosis of leg veins also subsided gradually.

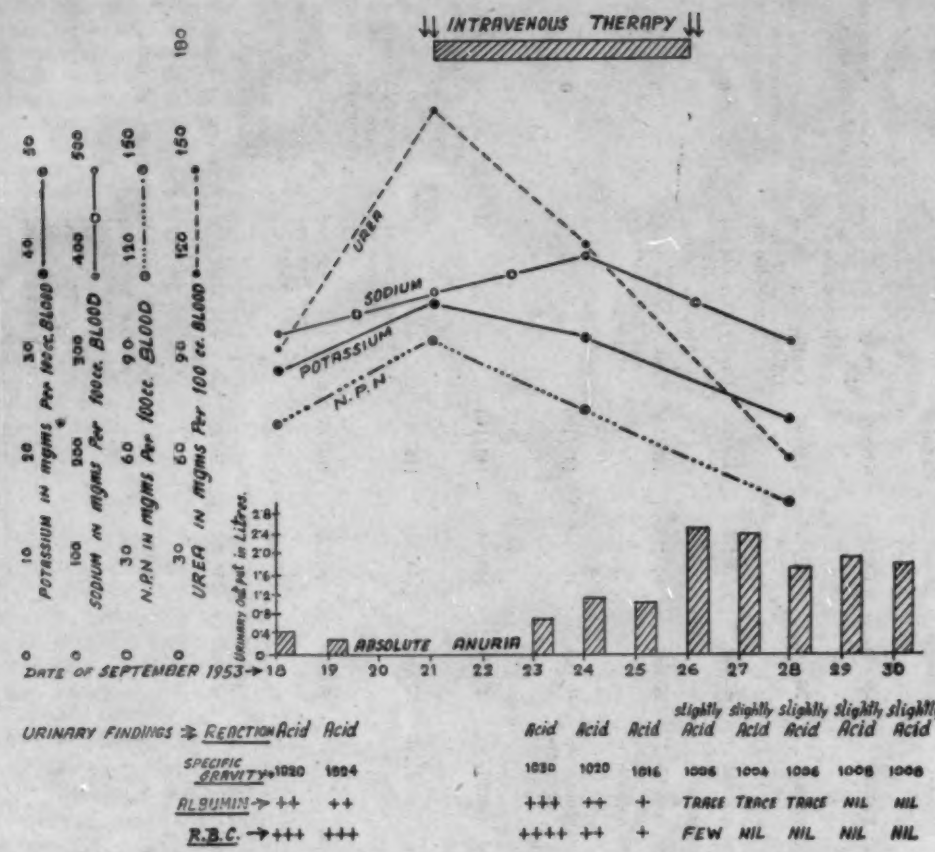
INTRAVENOUS THERAPY
UREA
SODIUM
POTASSIUM
N.P.N
POTASSIUM IN mgms. Per 100 c.c. BLOOD
SODIUM IN mgms Per 100 c.c. BLOOD
N.P.N IN mgms Per 100 c.c. BLOOD
UREA IN mgms Per 100 c.c. BLOOD
Urinary output in Litres.
ABSOLUTE ANURIA
DATE OF SEPTEMBER 1953 → 18 19 20 21 22 23 24 25 26 27 28 29 30
URINARY FINDINGS → REACTION Acid Acid Acid Acid Acid Acid slightly Acid slightly Acid slightly Acid slightly Acid slightly Acid
SPECIFIC GRAVITY → 1030 1024 1030 1020 1016 1006 1004 1006 1008 1008
ALBUMIN → ++ ++ +++ ++ + TRACE TRACE TRACE NIL NIL
R.B.C. → +++ +++ ++++ ++ + FEW NIL NIL NIL NIL

FIG. 1—BLOOD BIOCHEMICAL CHANGES IN GRAPHIC FORM AND IMPORTANT URINARY CHANGES.

drugs. The Bull's fluid with glucose and fat supplies 2500 calories. But in our attempt to give the patient sufficient fluid and glucose, we could supply nearly 2050 calories which was not insufficient to meet up the essential demands of the body tissues. The rationale of use of the following substances given by the intravenous route is discussed below :

10 per cent sodi bicarb solution 80 ml.—This was given with the idea of neutralising the acidosis resulting from anuria. The urine of the patient always maintained an acid reaction which persisted even after the onset of diuresis.

It has been claimed by Bull *et al* (1949) that the administration of electrolytes is not essential during the stage of anuria as the loss per excretion through other routes is minimum. They suggested that the electrolytes are to be used carefully when the diuresis starts to make good the loss of electrolytes. But in the present case only the sodi bicarb solution was given to neutralise the acidosis in anuria. The danger of administration of excess of sodium in anuria is pulmonary and/or cerebral oedema. In our present case we did not observe any untoward effect and the blood sodium level did not change considerably as shown in Fig. 1.

10 per cent calcium gluconate 40 ml.—It was given to the patient daily. The hyperirritability, muscular twitchings and convulsion in uraemia may be due to calcium deficiency as a result of increased phosphate level in blood in renal failure (Mullin *et al*, Resnik *et al*). Moreover, guanidine level in blood is raised in uraemia which causes muscular twitchings. So, calcium in this patient who was very irritable and restless might have played its role as a neurosedative to quieten the neuromuscular disturbances. Moreover, calcium is also known as cardiac accelerator and stimulator of cardiac muscle. In this particular case, the danger of hyperkalaemia might have been mitigated by the accelerator activity of calcium counteracting the inhibitory influence of potassium.

Vitamin C 1000 mg. and vitamin K 20 mg.—These were given daily to control haemorrhages. But their mode of action and their actual need in snake poisoning are still doubtful. Detailed investigations are essential to show whether there is any deficiency of vitamin C and/or prothrombin in blood in uraemic cases.

Fig. 1—Photograph of Case 5 showing the typical midline location of the growth in a patient of glossitis rhombica mediana.

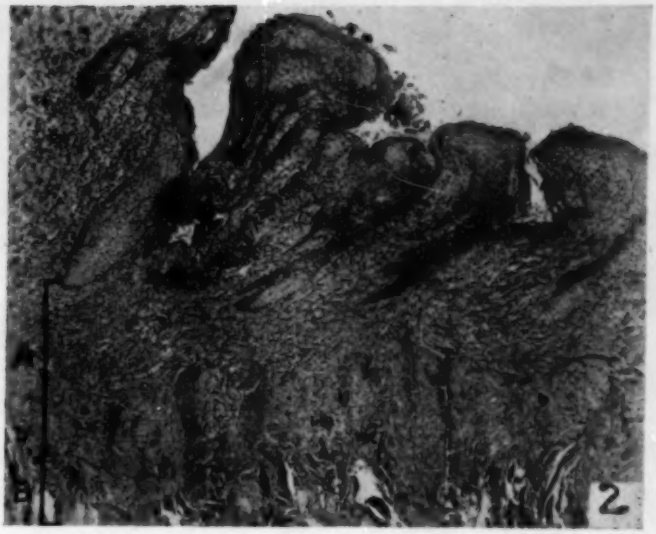

Fig. 2—Photomicrograph showing fibrosis in the subepithelial tissue (A) extending down to the muscle layer (B). Mallory stain × 25.

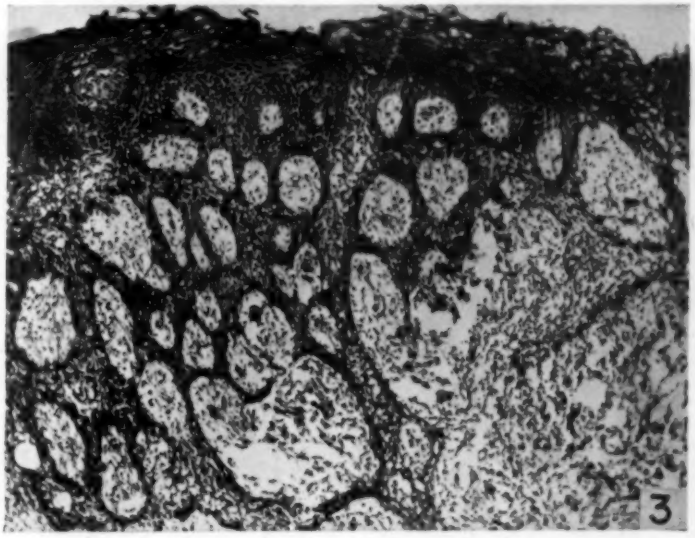

Fig. 3—Photomicrograph showing epithelial hyperplasia and subepithelial lymphocytic infiltration. H & E × 100

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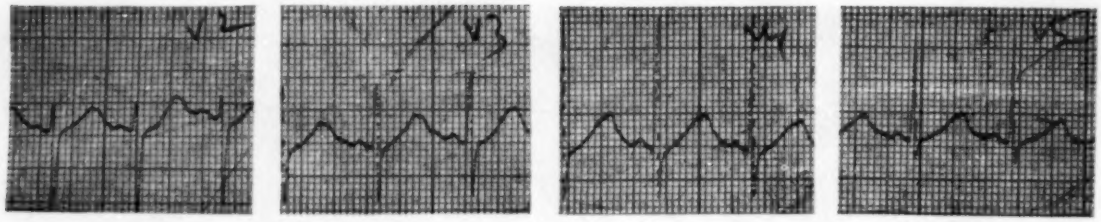

Fig. 2—E. C. G. 2. Wide QT interval with low and wide T waves showing the effect of hypopotassaemia.

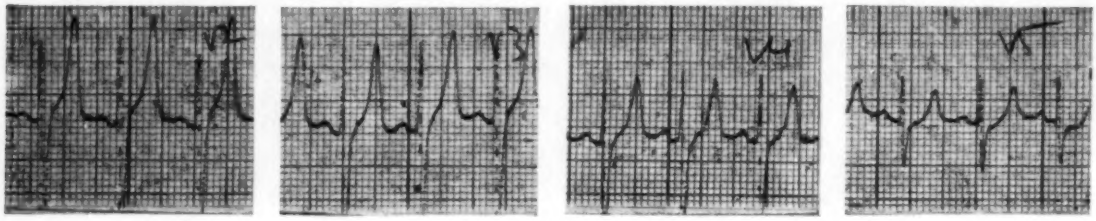

Fig. 3—E. C. G. 1. Low voltage, small or deficient P wave, wide QT interval with tall T waves showing the effect of hyperpotassaemia.

RAY AND BHATTACHARYA—*Acute Anuria with Vomiting and Hematemesis due to Snake Bite Poisoning (pp. 509-15)*

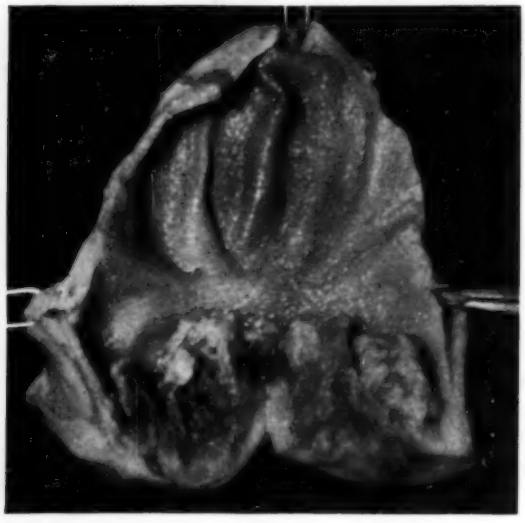

Fig. 1—Photograph of the specimen—Papillary adenocarcinoma of the gall bladder.

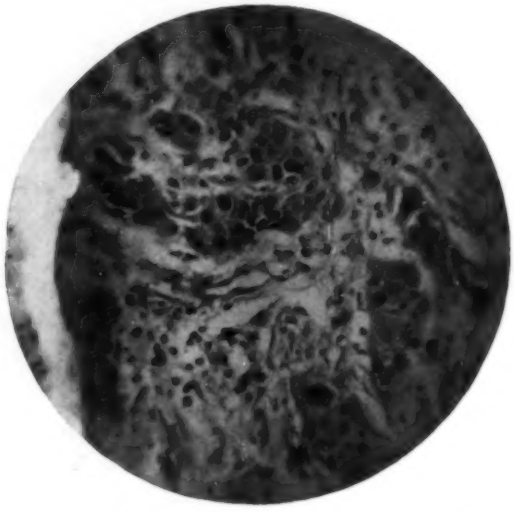

Fig. 2—Microphotograph of section showing cell characteristics. × 430

KANVINDE—*Carcinoma of the Gall bladder without Cholelithiasis (p. 515)*

Conclusion

In a case of acute anuria where the adoption of Bull's therapy was impossible due to excessive vomiting and haematemesis, our attempt to supply the essential caloric requirement of the body and to normalize the blood biochemistry level as far as possible with intravenous glucose, fluid, calcium gluconate, sodi bicarb, vitamin C and K were met with success. This mode of treatment needs a fair trial in cases of anuria complicated with repeated vomiting and/or haematemesis to tide over the critical period of renal shutdown.

Acknowledgment

We are extremely grateful to Drs. S. K. Mukherjee, Assistant Professor of Medicine (Paediatrics), Medical College, Calcutta, C. R. Das Gupta, J. B. Chatterjea and H. S. Chakraborty for their kind help, encouragement and advice; and to Dr. M. N. Sarkar, Principal and Superintendent, Medical College and Hospitals, Calcutta for permitting us use of the hospital records.

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CARCINOMA OF THE GALL BLADDER WITHOUT CHOLELITHIASIS

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A remarkable aetiological relationship of carcinoma of the gall bladder with gall stones has been stressed. The proportion of cases of cholelithiasis which develop cancer is estimated from 4 to 18 per cent. In a recent review of Tragerman gall stones were found in 79·8 per cent cases of gall bladder carcinoma. Mechanical irritation and digestive action of bile seems to play an important role in producing this condition. In some cases gall stones may have been small or passed earlier or the catarrhal inflammation which commonly leads to gall stones excites a cellular overgrowth without mechanical irritation of the formed stone. The case presented here did not show any evidence of cholelithiasis.

Case Report

A Hindu female aged 50 years was admitted on 20-12-1953 for painful lump in the right hypochondrium of ten days' duration. She had coffee coloured vomits on the evening before admission. No history of previous colicky pain or jaundice.

On examination there was tenderness but no rigidity, in the right hypochondrium and lumbar region. A diffuse lump $4'' \times 2''$ was palpable in the right hypochondriac region extending down upto the lumbar region. It was dull on percussion. There was no jaundice. Urine and stools were normal. Other systems showed no abnormality.

On operation a markedly thickened gall bladder was seen, 4 inches long, enlarged and adherent to the liver and the loops of intestines. A mass was felt in the fundal region. However, the whole gall bladder could be easily separated from the liver and the adherent loops of intestines and was removed. No glandular enlargement was detected. No secondaries seen in the liver. Patient made uneventful recovery and was discharged ten days after the operation.

The gall bladder 10 cm. long and 4 cm. broad, greyish white in colour showed tags of adherent omental tissue at the fundus. The fundus was distended by a firm mass inside, where the surface showed brownish discolouration. On opening, a large papilliferous growth 3 cm. × 4 cm. × 2 cm., light grey in colour was seen arising from the fundal wall. The growth was seen infiltrating the wall and at places reached almost to the outer surface. The superficial part of the growth showed evidence of necrosis and the bladder lumen was full of dirty greyish white necrotic material. No gall stones were found. The rest of the bladder wall showed general thickening. No evidence of cholesterosis detected (Fig. 1, *vide* Plate).

On microscopic examination the sections showed characteristics of papillary adenocarcinoma of the gall bladder with fair degree of infiltration of the wall. The growth presented elongated vascular papillae of connective tissue covered by cylindrical cells, while the base showed an alveolar structure with small alveoli of cuboidal cells infiltrating the muscular tissue (Fig. 2, *vide* Plate).

Acknowledgment

My thanks are due to Dr. M. D. Patel, for providing the clinical record of this patient and to Dr. M. D. Desai, Superintendent, Sheth Vadilal Sarabhai General Hospital, for permission to report the case.

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CALCUTTA, APRIL 1, 1955

WORLD HEALTH DAY

In what are called the "good old days" nations could keep themselves to themselves. There was little international intercourse and communicable diseases maintained more or less national boundaries. With the present mix-up all that has changed. Communicable diseases no longer amble quietly, they jump continents and skip oceans. The one body which has kept the global picture in view is the World Health Organisation. It is perhaps the greatest single organisation which has helped most in co-ordinating the activities, sometimes conflicting, of national governments in preventing disease and promoting healthier living conditions.

For several years past, the World Health Organisation has been observing the 7th of April as World Health Day. The objective of this day is to infuse a better sense of health consciousness in peoples of all walks of life throughout the world. The Day is not meant merely to alert the medical profession alone. Prevention requires the co-operation of many diverse peoples—the doctor, the nurse, the health visitor, the public health engineer and so on. But the most important person is not any of these but the ordinary man or woman. Prevention is a habit and the habit has to be formed in the ordinary people. Herein lies the importance of the Day. The WHO has given us every year a theme to dilate on. This year's theme is "Clean Water means Better Health".

India is a land of villages, notoriously lacking in safe and ample water supplies. Among the principal communicable diseases which levy a heavy toll of human lives in this country are cholera, dysenteries and typhoid fevers.

Given the necessary knowledge about the dangers of pollution and the mode of communication of diseases, the dangers from water-borne diseases may be minimised. The health centres in the community projects can do a lot to educate people in methods of healthful living.

While conditions in villages are admittedly bad, those in the cities are not much better. Cities are now so jampacked with humanity that existing water supplies are nowhere adequate to meet the needs of all. People have therefore no other alternative but to fall back upon dangerous sources of water to draw their supplies from.

All this is unfortunate. While attempts must no doubt continue to educate the people, safer and more adequate water supplies must at the same time be made available or the World Health Day's theme will be meaningless, at least to us in India.

LENTE INSULIN

Since the discovery of insulin in 1921, repeated attempts were made to get a preparation of insulin whose action would be both immediate and prolonged to keep down the blood sugar level throughout the day after a single injection. As a result of such efforts, we had protamine-zinc, globin and N.P.H. insulin. But their effect starts after a lag of a few hours, and they contain a third substance protamine or globin, which adds to the risk of possible allergic reaction due to insulin itself.

The most recent one in the list is *lente* insulin reported first by Hallas Moller *et al*[1] in 1952. Their preparation contains insulin, amorphous or crystalline, precipitated with zinc and suspended in an acetate buffer. Preparation of this insulin was based on the fact that insulin alone in the precipitated state, with a small quantity of zinc gives a protracted effect. Ordinary insulin cannot take up more than 0·8 mg. of zinc per 1,000 units but this new form in some way is made to take up 2 mg. The duration of action of these preparations depends on the size and form of the insulin particles. With the amorphous form, the action is shortest (about 16 hrs.) and this is branded as *semilente*; when the crystalline form (*ultralente*) is used, the longest period of effect (about 36 hours) is obtained. The mixture of these two forms (*lente*) has a period of action midway between the two (24 hours). Numerous reports about the efficacy of these preparations have been published.[2-6] Their main advantage is that the action starts within half an hour after administration and practically no untoward reaction has yet been reported.

This preparation of insulin opens up a new field of investigation in the management of diabetes. Immediate action after administration, avoids the separate prick of soluble insulin which is necessary with other varieties of long-acting insulin. The management of a case becomes easier both for the doctor and for the self-doctored patients. If this new variety can stand the test of time, the prevailing indecision over the types of insulin and their times of administration will pass over, much to the relief of the suffering patient.

[1] HALLAS-MOLLER, K. *et al*—*Science*, **116**: 394, 1952.
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[3] OAKLEY, W.—*Ibid*, **2**: 1021, 1953.
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CURRENT MEDICAL LITERATURE

Subdural Haematomas

CRAIG AND MILLER (*Minnesota Med.*, **37**: 484, 1954) from an analysis of 163 cases of subdural haematoma observed at the Mayo Clinic report:

The ages of the patients ranged from fifteen to eighty-eight years. One hundred and forty-seven of the patients were men and sixteen were women. There was a history of a mild or severe injury of the head in 132 cases. The haematoma was situated on the right side in seventy-three cases and on the left side in fifty-eight cases. In thirty-one cases, a haematoma was found on each side. In one case, the haematoma was situated in the posterior fossa.

The chief symptoms were as follows: headache in 137 cases; coma, drowsiness or psychosis in 106 cases; weakness of one or both sides of the body in ninety-two cases, and visual disturbances in fifty-two cases. Convulsions occurred in sixteen cases. Electroencephalography was used in eighty-one cases. Pneumoencephalography was used in forty-three cases, and it revealed a shift of the ventricular system away from the lesion in forty-two of the forty-three cases.

Two hundred and two operations were performed in the entire group of 163 cases. In forty-five cases, the initial operation was a craniotomy; in the 118 remaining cases it was performed with a burr. A second exploratory operation was necessary in thirty-nine of the 163 cases.

In twenty-four cases, the patients died within four days after the operation. The convalescence was uneventful in ninety-eight cases. In thirty-two of the 163 cases, postoperative examination revealed a neurologic or mental deficit of 10 to 20 per cent.

The primary objective of the surgical treatment of subdural haematoma is evacuation of the haematoma to allow the compressed brain to expand beneath the clot. This may be accomplished by craniotomy or trephination. If the haematoma is so solid that it cannot be evacuated through openings made with a trephine, or if the membrane of the haematoma refills after trephination, craniotomy should be performed. Since subdural haematomas occur bilaterally in 20 to 30 per cent of all cases of this lesion, an opening should be made on each side of the skull.

Spinal Tumors

BLOOM AND OTHERS (*Brit. M. J.*, **1**: 10, 1955) in dealing with the early diagnosis of spinal tumors based upon a study of 36 cases at the Military Hospital for Head Injuries, Oxford, write:

The average delay between the first consultation and operation was 6·4 months. Common diagnostic errors were 'fibrositis' or 'rheumatism' in 28 per cent of cases, prolapsed intervertebral disk or 'sciatica' in 28 per cent, and 'neurosis' in 25 per cent.

The most frequent complaint was backache and/or root pain, occurring in 81 per cent of cases; in 61 per cent it was the initial symptom. In five cases there were only minimal or doubtful neurological signs, although pain had been present for nine months or more.

The most frequent neoplasm was the neurofibroma (41 per cent). An unexpectedly large number of metastatic tumours was present (22 per cent), most of which appeared to be of bronchial origin; three of these tumours occurred in patients between 17 and 19 years of age. A metastatic lesion should be suspected if the history is short and the clinical picture advanced.

Reference is made to the ancillary investigations, and attention is drawn to the value of lumbar puncture in early diagnosis, especially in doubtful cases. Evidence of spinal block was obtained in 76 per cent of cases, and in all 35 patients whose cerebrospinal fluid was examined the protein content was raised.

Lumbar puncture may be the only way of excluding a tumour with any confidence in patients with persistent back or root pain for which there is no obvious cause. The possible dangers of the procedure are negligible, except in rapidly progressive cases and those with suspected cervical tumours, the investigation of which should be delayed until neurosurgical aid is available.

Electrolytic Losses with Biliary Fistula

CASS AND OTHERS (*M. J. Australia*, **1**: 165, 1955) write that measured over five-day periods after operation, the electrolyte and water losses from a biliary fistula are of the same order as those from continuous gastric aspiration.

With the uncorrected loss of biliary electrolyte, sodium is lost from the body fluids in excess of chloride. Base deficiency with acidosis results, contrasting with the chloride deficiency and alkalosis of uncorrected gastric loss.

A syndrome, here termed the post-choledochostomy acidotic syndrome, is described and its treatment is given.

The symptoms of the post-choledochostomy acidotic syndrome are essentially those of sodium chloride depletion, with superadded acidosis, since more sodium is lost than chloride. Bland emphasizes that the symptoms of sodium chloride deficit are unfortunately vague and unimpressive. There are anorexia, apathy and weakness, but little else until the depletion is far advanced, when stupor deepened and there are attacks of sudden vasomotor collapse especially on sitting up. These depend on decrease in the vascular compartment's volume with vascular hypotension.

Treatment of post-choledochostomy acidosis presents no problem. Awareness of the possibility of its existence in the stuporose, failing patient is all that is necessary. Biochemical confirmation is obtained in the low urine chloride excretion, and the low serum sodium and chloride contents and carbon dioxide combining power, together with the raised blood urea level. Correction of the deficit by oral or intravenous sodium chloride therapy characteristically produces a dramatic improvement in mental and physical status.

With awareness of the problem, prevention is easily achieved. The daily loss from the fistula is measured and replaced intravenously by an equal volume of saline. Thus about 500 cubic centimetres of bile usually drain daily, and this can be replaced by half a litre of isoto-

nic saline, or if the patient is being fed orally, four grammes of salt are given in a mixture.

Conservative versus Radical Treatment of Bladder Tumours

BARNES AND OTHERS (*M. J. Australia*, 1 : 197, 1955) basing on a study of 245 cases of bladder tumour observe that there is 52 per cent five-year survival rate after conservative treatment, mostly by transurethral resection. The use of radon seeds after transurethral resection does not increase the survival rate. This compares with a maximum of about 20 per cent five-year survivals after cystectomy as reported by other authors. The hazards of uretero-sigmoidostomy are an important factor in reducing the survival rate after cystectomy.

Most bladder tumours can be treated by properly performed transurethral resection more successfully than by any other means. Meticulous technique, the recognition of tissue as seen through the resectoscope, and the use of an isotonic irrigating fluid are necessary. Tumours larger than seven centimetres in diameter are more suitable to transvesical resection and electrocoagulation, and those located in the ventral bladder wall should usually be removed by partial cystectomy. Careful, persistent follow-up examinations and endoscopic destruction of recurrences are essential to obtain the best results.

Radioactive Colloidal Gold in Papilloma of Bladder

ELLIS AND OLIVER (*Brit. M. J.*, 1 : 136, 1955) give in the following the summary of their observations :

A technique is described for the treatment of multiple villous papillomatosis of the bladder whereby some 300 mc. of radioactive colloidal gold (Au^{198}) may be introduced per urethram so as to deliver a dose to the bladder epithelium of about 3,000 r in three hours. The recommended course is two such treatments with about two months' interval.

The procedure is safe for the patient and for the staff, if properly carried out.

It has caused complete disappearance for fifteen months of myriads of papillomata in a 67-year-old man, leaving him symptom-free.

In cases unsuitable for complete treatment by this method it may be used to bring about the disappearance of multiple small tumours and to stop haemorrhage. Accurate cystoscopic examination may thereby be rendered possible and the surface of a carcinoma devitalized preparatory to subsequent cystostomy.

Triethylene Melamine in Bronchogenic Carcinoma

SALINE AND BAUM (*J.A.M.A.*, 156 : 1493, 1954) write that triethylene melamine (TEM), a nitrogen-mustard-like compound, is indicated in the palliative therapy of bronchogenic carcinoma with superior vena caval obstruction. Careful control of the dosage and follow-up are necessary to avoid serious bone marrow depression. The average dosage was 5 mg. given daily for a period of 4 days, with a maintenance dose of 2·5 to 5 mg. every one to six weeks, depending on the clinical response and haematological effect.

Relief of Pain in Incurable Cancer

MAHER (*Lancet*, 1 : 18, 1955) writes that 37 cases of incurable cancer were treated by intrathecal phenol. Relief of pain was obtained in 29 cases. Success apparently depended on whether single or combined nerve-groups were involved.

Phenol in glycerin or propylene glycol was used with success at all spinal levels, including the cervical region.

The immediate aim was to produce fixed skin anaesthesia over the painful area.

Spinal cord block was attempted in 3 instances, and gave relief.

Cancer Detection

HITCHCOCK AND AUST (*Minnesota Med.*, 37 : 243, 1954) give in the following lines the summary of a report from the Cancer Detection Centre, University of Minnesota :

During five years' operation of the Cancer Detection Centre at the University of Minnesota ninety-one malignancies were found in 5,352 examinees. A total of 11,343 examinations were performed. This represents seventeen cancers per 1,000 patients examined (1·7 per cent), or 7·9 cancers per 1,000 examinations performed.

Forty-six examinees with cancer were symptom free for the organ system in which the lesion was found. Forty-five had symptoms indicating a likelihood of cancer in the organ or organ system involved. In the asymptomatic group twenty-four cancers were found at recheck examination, indicating the value of repeated examinations to detect malignancies in their earliest stages.

Only in cancer detection centres, or cancer prevention clinics are large numbers of persons surveyed for cancer while they are without symptoms of disease. It seemed of value to emphasize the difference in survival between symptomatic and asymptomatic examinees found to have cancer in this study.

Three of six asymptomatic gastric cancer patients are alive and well up to four years after surgery. There is one survival among five gastric cancer patients who were symptomatic at the time of diagnosis. Of thirteen patients with colon cancer who were free of symptoms at time of diagnosis, eleven are living and well (seven over three years). Only one of the five colon cancer patients with symptoms at time of diagnosis is living (two years). These results appear to substantiate the increased value of early diagnosis in terms of survival.

Twenty-four per cent of our patients had pre-cancerous lesions. The value of treatment of these lesions in the prevention of cancer is incalculable.

Of all cancers developing in our examinees during this five years, 9 per cent are considered failures of the Detection Center method. Roentgen ray techniques failed in 6 per cent of the thirty-four patients in whom the diagnosis was established by this modality. Misinterpretation of x-ray changes was the responsible factor. Of the cases detected by means of physical examination and laboratory studies 8 per cent must be considered as failures for this method.

It is believed that several types of serious malignancy can be identified in advance of their usual signs and symptoms through the application of a well conceived, routine, cancer detection examination performed at yearly intervals.

CURRENT TOPIC

PROGRESS OF PHARMACOLOGY AND ITS CONTRIBUTION TO MEDICINE†

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Growth of Materia Medica

Pharmacopoeia owes its inception to the works of Dioscorides who was considerably influenced by the systematic botanical knowledge imparted for the first time by Theophrastus (370-286 B.C.). Contrary to tradition, Dioscorides in 57 A.D. classified his materia medica by substance rather than by disease. He described carefully the individual drugs and also their mode of preparation and administration.

One century later, Galen (131-201 A.D.) developed an elaborate system of polypharmacy which was destined to influence medicine for some fifteen hundred years.

The polypharmacy, *i.e.*, combinations of so-called therapeutic materials was the natural outcome of the belief in the greater strength of the multitudes as compared to that of the individuals. Galen wrote as many as thirty books on pharmacy alone. It was he who initiated the use of simple vegetable products which are still known as "galenicals". He prescribed hyoscyamus, hellébore, colocynth as well as wine, honey and turpentine. Probably his greatest single contribution to therapeutics was tincture of opium, later named laudanum by Paracelsus.

Paracelsus (1493-1541) who became the Professor of Medicine at the University of Basel, started his university career by making bonfire of the total works of Galen. He challenged Galen's theory of four humours (fire, air, water and earth). He was a non-believer in demoniacal possession and supernatural origin of diseases. He ridiculed the absurd mixtures of herbs advocated by Galen and popularised salts of potassium sulphate and simple preparations of sulphur, iron, arsenic and antimony which were chemical entities, the knowledge being imbibed from the then alchemists.

By 1546 the need for standards and official regulation of drugs was recognised. Early genuine Pharmacopoeia (Dispensatorium) was prepared by a young man Valerius Cordus. The Dispensatorium contained references of five hundred new species and this was published by authority of the Senate of the City of Nuremberg.

In and about 1500 B.C. the Hindu Medicine was also similar to that in the European countries. The science of medicine, *i.e.*, Ayurveda, however, made considerable progress at the beginning of the Christian Era mainly in the hands of two Hindu physicians, Charaka and Susruta (5th century A.D.), Susruta wrote on many subjects and his description of surgical techniques and instruments inspire reverence even today. It may be observed that he (Susruta) associated malaria with mosquitoes, human plague with epizootic of rats, and not the least interesting was the association of phthisis with haemoptysis, cough and fever.

Growth of Pharmacology

Pharmacology is the science of action of drugs. It developed in the early days from the study of poisons which being potent substances produced definite effects as compared to so-called therapeutic substances which were mostly less potent. It was Mithridates, King of Pontus, in 2nd century B.C. who centred his attention on snake venoms. In order to find a suitable antidote, Mithridates studied the effects of various poisons by administering them to his slaves and other criminals and claimed that he had thus discovered an antidote for every venomous reptile and every poisonous substance. The drug known as *Mithridaticum* subsequently developed in the hands of later physicians into *Theriacs* containing some fifty ingredients including viper's flesh and all kinds of vegetable products. To give Mithridates his due, it was he who discovered that he could immunise himself against certain poisons by gradually increasing doses. Today "acquired tolerance" goes by his name as "Mithridatism".

Paracelsus believed that there was a specific remedy for each disease, if only the remedy could be found. Of all the specifics he advocated only one was approaching the truth, and that was mercury in syphilis. Widespread application of Paracelsus's medicaments, which being potent mineral substances caused more damage than good; whereas galenicals, being mostly less potent at least did little harm if not did any good.

Systematic study of gross toxicology was not done till the 17th century, when Johannes Wepfer (1676) produced tetanic symptoms in dogs by large doses of nux vomica. These observations were followed by those of Anton Storck (1731-1803) who studied the effects of hemlock, stramonium, aconite and hyoscyamus.

Development of rational therapeutics although attempted on several occasions could not be materialised due to lack of proper knowledge in physiology and pathology. Consequently in spite of early toxicological study, the heroic symptomatic so-called allopathic treatment of James Gregory (1753-1821) could flourish all over the world. The favourite remedies were blood letting, emetics and purgatives and these were used until the main symptoms of the disease were suppressed. Thus malaria and dysentery were treated by purging with twenty grain doses of calomel until collapse was manifest. Blood letting was so frequently practised that thirty-two million leeches were used in a single year in France. At the commencement of 19th century, Hahnemann justifiedly revolted against this unsatisfactory and dangerous system of therapy and laid down the principles of Homoeopathy. Both homoeopathy and allopathy were devoid of any scientific basis; but there was no doubt that the former did less damage than the latter. It must be admitted that modern therapeutics has inherited from allopathy the knowledge of many valuable drugs and from homoeopathy, the remarkable power the body possesses of healing itself, if given a chance in suitable cases.

The advance in the knowledge of chemistry and biology in the late 18th and early 19th century led to the development of modern pharmacology and therapeutics. Thus isolation of morphine from opium by Friedrich Serturner in 1806 acted as a stimulus for search for other essential principles in various crude drugs, then available. This was followed by isolation of emetine from ipecacuanha (Joseph Pelletier, 1788-1842), quinine from cinchona (Caventou, 1795-1877) and strychnine from nux vomica (Magendie, 1783-1855).

Wohler in 1828 brought revolution in the field of organic chemistry by synthesising urea from ammonium cyanate in the laboratory. Thousands of new drugs, plastics, perfumes, which are now prepared are the results of synthetic organic chemistry, which owed its inception to this experiment.

Modern School of Pharmacology

It was Oswald Schmiedeberg (1838-1921) who transformed the old fashioned materia medica into modern pharmacology as an independent science. He became the Professor of Pharmacology at Strasbourg and to him came students from all parts of the world. Among his eminent pupils were Abel, Cushny, Sollmann, Meyer, Heubner.

John Jacob Abel is the Father of Modern American Pharmacology. He was the pioneer in isolating the first hormone, adrenaline from adrenal medulla in 1900. The

† Being Capt. Narendra Nath Dutta Memorial Oration for 1954.

isolation of the posterior pituitary hormone in 1919 and crystalline insulin in 1926 are the two most outstanding contributions of Abel and his co-workers.

Whereas in Great Britain, Arthur Robertson Cushny (1868-1926) who specialised in drugs affecting the heart and circulation and the kidney, together with enthusiastic Dale and Dixon exerted a world wide influence on the development of the science of pharmacology. I remember with gratitude the inspiration I received while working under Cushny in 1914 at the University College, London.

Pharmacological Study in India

In India, Col. R. N. Chopra may be classed with Abel as the Father of Modern Indian Pharmacology. And it is no small credit to him to produce quite a large band of pharmacologists who adorn many important and responsible posts. To mention a few, we have Dr. B. Mukerji, Head of the Central Drug Research Institute at Lucknow. Like his teacher Dr. Mukerji also trained some pharmacologists who are holding responsible posts. Dr. M. D. Chakravarti, Head of the Central Drugs Laboratory, Dr. J. C. Gupta, who followed the foot steps of his master and adorned the Chair of Pharmacology at the Calcutta School of Tropical Medicine and last but not least Capt. Premankur De whose death we all mourn. India made some solid contribution specially evaluation of some of the indigenous drugs and placing them on scientific basis. I may mention that for the first time it has been possible for me to isolate some fractions from *Terminalia arjuna* which produce action on the heart thus confirming time honoured opinion that this drug enjoyed amongst the Hindu physicians as a cardiac tonic. The same may be said of *Saraca indica* or Ashoke which also has been found in my laboratory to contain certain active principles having definite action on the uterus.

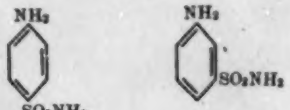
Mechanism of Drug Action

I will not tax your patience by discussing in detail the drug action. I will just make a survey of the present conception how chemical composition or constitution and chemical substitutes and metabolite analogues influence the action of various drugs. These sometimes nullify, modify or intensify the original action of drugs. Because of this knowledge it has been possible not only to synthesise many new products but also we are able to explain how the different compounds produce their specific effect.

We will first consider how the chemical composition remaining the same, molecular arrangement alters the action of a drug.

Let us take some familiar examples.

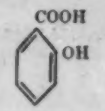
Sulphanilamide is *p*-aminobenzene sulphonamide with the following formula :



Sulfanilamide — Meta derivative (valueless in therapy)

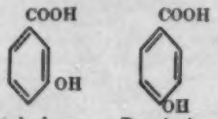
It becomes practically useless when the SO_2NH_2 is placed in meta or ortho position. This is possibly due to the fact that the original structure resembles p-aminobenzoic acid, which is at least one of the factors responsible for the anti-infective activity. The meta or ortho derivatives do not enjoy this spatial relationship to PABA.

Again, orthohydroxybenzoic acid, i.e. salicylic acid has the following formula—



Orthohydroxybenzoic acid (Salicylic acid)

Its sodium salt is used in the treatment of rheumatic fever. But the isomeric derivatives are useless tor fhe purpose. They are—

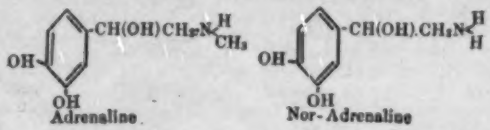


Meta hydroxybenzoic acid — Para hydroxybenzoic acid

Méta hydroxybenzoic acid and Para hydroxybenzoic acid.

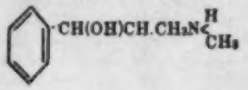
I will now discuss how addition or deletion of some molecules alters the action of a drug.

Let us take adrenaline and nor-adrenaline—



Adrenaline — Nor-Adrenaline

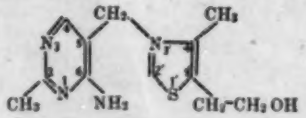
It will be observed that nor-adrenaline differs from adrenaline in the absence of N-methyl group with the result that it is a vasoconstrictor with little effect on the heart specially its rate and therefore of cardiac output.



Ephedrine

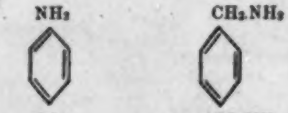
Again ephedrine differs from adrenaline by the absence of the two hydroxyl groups and the presence of an extra methyl group. These make it more stable.

If the methyl-group is removed from the 2-position in the pyrimidine ring of thiamine the vitamin activity



drops to 1/22 of its former value. If the methyl-group is removed from the 4'-position of the thiazole ring, its activity drops to 1/82, and if inserted in the 2'-position of that ring, its activity completely disappears.

Let us take another example, Maphenide or Marfanil which is chemically related to sulphanilamide with the difference that the amino-group is not attached



Sulfanilamide — Maphenide

directly to the benzene ring but is separated by a methylene-group-CH_2. Its antibacterial effect is not antagonised by pus or PABA.

But the most important advance in this direction has been selective antagonism by particular metabolites, or what is popularly understood as biological or substrate competition.

To understand this we should first have some idea regarding what is a metabolite and a metabolite analogue.

Metabolite is any substance which is involved in the biochemical reactions by which cells assimilate food and use the resultant energy for growth and reproduction. The most important metabolites for our purposes are those which are present in the smallest amounts, since it is more easy to antagonise these than which are present more abundantly.

Metabolite analogue is a substance which differs from a metabolite only by a small degree of chemical change. The most familiar example of a metabolite analogue is sulphanilamide which antagonises the action of chemically similar substance, p-aminobenzoic acid which is a metabolite of great importance to micro-organisms.

Many metabolite analogues are known, and Woolley lists forty metabolites for which antagonistic analogues have been made. For instance, pyrithiamine is a competitive antagonist of the vitamin thiamine and produces thiamine deficiency in mice faster than can be accomplished by feeding on thiamine-free diet. It is now believed that almost all drugs will be found to exert their ultimate biological effect by interfering with the working of the enzymes. The important part which metabolite analogues play in the cure of infectious diseases were not recognised until Fildes pointed out the relationship of sulphanilamide to *p*-aminobenzoic acid. This acted as an impetus for further investigation along these lines not only to explain the action of many but also to test many such analogues.

When it was learnt that pantothenic acid dramatically increased the survival time of malarial parasites in *vitro*, hence an important natural metabolite for these organisms, various analogues of pantothenic acid were tested as possible antimalarials.

Bernheim first pointed out that benzoic acid and salicylic acid increased the oxygen uptake of the *Mycobacterium tuberculosis* suggesting that these or similar substances might be important metabolites of these organisms. Assuming that salicylic acid was a natural metabolite, Lermann found that of all the substances which act by inhibiting the bacterial metabolite by a mechanism of substrate competition, p-aminosalicylic acid was found to be most active.

Autonomic Nervous System

Much light has been thrown within recent years regarding the function of the autonomic nervous system and a short discussion will not be out of place. The most important advance has been in the field of chemical mediation of the various nerve impulses. Otto Loewi first demonstrated different chemical transmitters, namely acetylcholine and adrenaline which were released when the autonomic nerves were stimulated. Further, the distribution of nerve fibres which are cholinergic (i.e. liberate acetylcholine) and adrenergic (i.e. liberate adrenaline-like substance or sympathin) does not correspond with the anatomical division of parasympathetic or sympathetic respectively. Cholinergic nerves comprise the following: (a) motor nerves to the skeletal muscles; (b) all preganglionic nerves belonging to both sympathetic and parasympathetic systems; (c) all postganglionic fibres of the parasympathetic system; and (d) postganglionic fibres of the sympathetic supplying the sweat glands and certain blood vessels. Whereas only the postganglionic fibres of the sympathetic system except those already mentioned are adrenergic. It has further been observed that the transmitter of adrenergic impulses is not adrenaline but its lower homologue nor-adrenaline or sympathin which is also liberated from the suprarenal medulla.

In their passage through the central nervous system to the effector organ the impulse passes through the preganglionic fibres where acetylcholine is liberated in both sympathetic and parasympathetic divisions. Acetylcholine so liberated stimulates the ganglion cells, from which arise nerve impulses which pass along the postganglionic nerve fibres and in turn liberate transmitter agents from their nerve endings. The postganglionic parasympathetic fibres produce and liberate acetylcholine, whereas most of the postganglionic sympathetic liberate sympathin or noradrenaline. These substances then act upon organs innervated by the autonomic nervous system.

Although acetylcholine is liberated at the autonomic ganglia, the end plates of skeletal muscles, and at the postganglionic nerve terminals of the parasympathetic, there is significant variation in the behaviour of response at these levels with certain drugs which suggest existence of difference in the receptor or effector organs at sites concerned. Muscarine, for instance, stimulates the postganglionic *cholinergic* fibres only including those supplying certain blood vessels and sweat glands (muscarine effect); nicotine on the other hand affects not only the ganglion cells but also the nerve ends of the skeletal muscle without affecting the postganglionic fibres. Moreover, its effect is complicated inasmuch as it produces primary stimulation followed by paralysis.

The effects of stimulation of sympathetic or parasympathetic are short lived since both acetylcholine and sympathin are hydrolysed by enzymes cholinesterase and amine oxidase respectively. Cholinesterase hydrolyses acetylcholine to choline and acetic acid and thus it loses its physiological action and is of little value clinically. Similarly cocaine acts by inactivating the enzyme amine oxidase responsible for the destruction of adrenaline. While certain drugs which mimic the action of adrenaline, act by competing with adrenaline for the enzyme amine oxidase. Ephedrine belongs to this class.

Loewi demonstrated that the physostigmine prolongs the effect of cholinergic nerve impulse by blocking the action of cholinesterase thus preserving acetylcholine. This observation was followed by intensive search for compounds having anticholinesterase action and neostigmine was introduced.

Recently several compounds, Di-isopropylfluorophosphonate (DFP), Hexaethyltetraphosphate (HETP) and Tetraethylpyrophosphate (TEPP) have been synthesised which also block the action of cholinesterase but more efficiently. All these drugs are classed as "anticholinesterase" or acetylcholine conservers.

There is however difference in action between physostigmine and neostigmine on the one hand and the newly introduced phosphonate compounds on the other. Whereas the action of neostigmine and physostigmine is reversible and act by substrate competition with acetylcholine for the enzyme cholinesterase; DFP and similar compounds act by irreversible inactivation of the enzyme, consequently the effect is more prolonged and recovery of cholinesterase activity can only occur after fresh synthesis of the enzyme by the tissues.

Besides the group of drugs known as "anticholinesterase" another important group is acetylcholine antagonists, to which belongs atropine, and quite a number of therapeutically useful compounds acting by opposing the action of acetylcholine have been introduced.

Muscle Relaxants

Drugs belonging to this group counteract the action of acetylcholine on skeletal muscle only without having any significant effect on other types of tissue. Besides tubocurarine, several compounds have been synthesised. They are Decamethonium, Suxamethonium and Gallamine Triethiodide or Flaxedil.

It has been observed that if acetylcholine in high concentration is injected suddenly into an artery supplying a small group of muscles it will produce powerful contraction or fibrillation of the muscles followed by paralysis

for a short period, i.e. the impulses in the motor nerve fail to pass to the muscle. It is probable that the amount of acetylcholine reaching the muscles is great and it takes a little time for cholinesterase to destroy it. Till this happens the muscle membranes remain depolarised and will not respond to a stimulus until repolarisation occurs. Acetylcholine liberated at the myoneural junction depolarises the muscle membrane, and the muscle remains inexcitable until acetylcholine is destroyed by cholinesterase which is followed by repolarisation, when the muscle again becomes excitable. Two types of muscle relaxants are available.

Depolarising relaxants.—Decamethonium and Suxamethonium belong to this group. They probably act in the same way as excess of acetylcholine. Since physostigmine and neostigmine act by inactivating the enzyme which hydrolyses the normal depolarising agent, acetylcholine, these do not antagonise this group of drugs.

Anti-depolarising relaxants.—To this group belong tubocurarine and gallamine triethiodide (Flaxedil). They do not depolarise the muscle membrane, nor prevent liberation of acetylcholine but the effects may be overcome by physostigmine or neostigmine, which increase the concentration of acetylcholine at the end plates. It is suggested that these compounds offer competition to acetylcholine by getting themselves attached to some chemical receptor group to which acetylcholine is normally attached thus preventing acetylcholine from producing normal depolarising effect.

These drugs are used to produce relaxation of skeletal muscles and are used in various spastic or convulsive conditions and during surgical operations as adjuvants of general anaesthetics.

Ganglion Blocking Agents

These drugs oppose the action of acetylcholine on transmission through autonomic ganglia and produce fall of blood pressure. To this class belong Tetraethylammonium compounds (TEA) and methonium compounds (Penta and Hexa-methonium). While these blocking agents act preferentially on the autonomic ganglia, tubocurarine, decamethonium compounds and flaxedil have predilection for the end plates of skeletal muscle. Whereas the effect of tetraethylammonium salts is transient lasting for half to one hour, that of methonium compounds remain for six to eight hours. They produce greater fall of blood pressure in the erect position, less in the sitting posture and still less in the recumbent position. Besides development of tolerance, visual disturbance from pupillary paralysis, nausea, constipation, or even paralytic ileus are common. Sometimes the fall of blood pressure is too much to cause death and some cerebral thrombosis has been found in post-mortem.

Ganglion blockers have the widest therapeutic application in the field of surgery. Besides their use as muscle relaxant, methonium salts are being used to block transmission of sympathetic ganglia causing relaxation of the muscle of the vessels and fall of blood pressure to such an extent that a bloodless field of operation can be secured by suitable postural adjustment of the patient. They have also been used in cases of gastric and duodenal ulcer.

With penta-methonium or hexa-methonium compounds it is possible to maintain reduction of the standing blood pressure which will give relief to many of the unpleasant symptoms. These compounds have given great relief in acute dyspnoea from left ventricle failure which sometimes happens to hypertensive patients.

Modern Hypotensive Drugs

Treatment of hypertension is not satisfactory, possibly because we do not know what exact changes are responsible for this condition. Goldblatt first pointed out that ischaemia of the kidneys produces persistent rise of blood pressure, and this has been attributed to an enzyme called "renin", discharged into the circulation, which is inactive as such but becomes active by being converted into *hypertensin* by the interaction with a substance called *hypertensinogen*, a component of alpha-globulin fraction of blood plasma. This hypertensin is destroyed by the normal kidney and plasma, whereas it remains unaffected in ischaemia or disease of the kidney. Neither renin nor hypertensin have been isolated from the blood of patients suffering from essential hypertension. It is generally agreed that vaso-constriction from which these patients suffer is neither the result of excessive sympathetic activity nor to any organic changes in the arterioles. While patients suffering from arteriosclerosis often get kidneys affected, on the other hand patients suffering from chronic nephritis often suffer from hypertension and arteriosclerosis.

In primary or neurogenic hypertension there is vasoconstriction due to biochemical imbalances in the organism and the vasoconstrictor centre is stimulated. Supplemental factors are discharge of noradrenaline which is a powerful vasoconstrictor from adrenaline medulla, increased secretion of vasopressin from posterior pituitary. The anterior lobe may secrete an increase of ACTH which again may stimulate the secretion of adrenal cortex steroids resulting in retention of sodium by the kidney.

Essential hypertension is treated by the administration of adrenergic blocking agents or sympatholytic group of drugs. Although their value is limited, real solution lies in this direction and it is possible that some new compound of this class will be forthcoming which will be more effective than any so far available. *Rauwolfia serpentina* is perhaps one such.

The drug which has received wide recognition at the present moment is *Rauwolfia serpentina*, first brought into prominence by Col. R. N. Chopra and his co-workers. The great possibilities of this drug acted as an impetus and it is being investigated in different laboratories all over the world. Besides hypotensive property it possesses a central sedative effect. In fact it has been used in India for the treatment of insanity. True mechanism of its action is not yet settled. However, Werner and his colleagues at the School of Tropical Medicine suggested a central vaso-motor depression and sympatholytic action. At the present moment it is rather difficult to evaluate the different preparations available in the market owing to lack of standardization as also due to variability of individual response.

Chemotherapy—Its Evolution and Progress

"If I ask the pharmacologist" Paul Ehrlich used to say "to tell me how quinine produces its effects, he tells me how it acts on a frog's muscle, or on a mouse's brain, or on living cells as a general protoplasmic poison. But that is not what I want to know. I want to know how quinine specifically attacks the malaria parasites, causing them to disappear from the blood of the sufferer from malaria—how otherwise harmless doses of it thus cure the patient, not how excessive doses would poison him; and the pharmacologist cannot tell me."

Ehrlich being a chemist had a different angle of vision from the pharmacologists of his time. He introduced the term "chemotherapy" to describe the cure of infectious diseases without injury to the host, a new conception which led to the development of large series of synthetic compounds. These compounds, he believed, like the antitoxins and antibacterial substances would have a maximal affinity for the toxic agent or parasite, and a minimal affinity for the organs of the infected animals or human being, in other words would possess maximum "parasitotropic" and minimum "organotropic" property.

Ehrlich differentiated between immunotherapy (i.e., therapy with vaccines and sera) and chemotherapy. While immunotherapy is concerned in strengthening the defences of the body, his conception of chemotherapy was a direct attack on the parasite. The problem as he saw it, was to find chemicals with much stronger affinities for the parasites than for the tissues of the host.

Since certain dyes were able to stain specifically certain cellular elements, a search was made to find a substance which will unite with and destroy the parasitic agents of the disease without injuring the cells of the body. But substances which are toxic to the parasite are also toxic to the body tissues. The object of chemotherapy is to find substances which the tissues will stand in large doses, but will be fatal to the infecting organism in small doses, i.e., will possess favourable chemotherapeutic index.

Ehrlich in 1891 tried methylene blue as a cure against malarial parasite. But this was unsuccessful for various reasons. Subsequently when the technique of experimental transmission of trypanosome into susceptible animals became known, Ehrlich, in 1903 in collaboration with Shiga, tried trypan red in trypanosomal infection in mice. But this was unsuccessful since this dye failed to have any effect in natural trypanosomal infection in man and higher animals. Ten years after the death of Ehrlich, Elberfeld prepared "Germanin" or Suramin (Bayer 205), a derivative of the red dye and this compound is still the most potent agent we possess against human trypanosomiasis.

In the year 1905 atoxyl was introduced which was found to possess a curative effect on trypanosomal infection in mice, and was used both for the treatment of trypanosomiasis and syphilis of man, but had to be abandoned because of its toxic properties and the tendency to produce blindness. Ehrlich however continued his search to find a suitable chemotherapeutic agent for the cure of syphilis.

After hundreds of experiments Ehrlich with the assistance of Hata discovered the drug known as "Salvarsan" or 606 (Arsphenamine) which was followed by the introduction of a modified compound Neoarsphenamine or 914. These two compounds approached the ideal of Ehrlich in possessing maximum parasitotropic effect with minimum organotropic property. It was found that these arsphenamines produced their spirochaeticidal action by being converted into amino-oxyphenyl arsenoxide or Mapharside, and this compound has practically replaced both salvarsan and neosalvarsan, and has been introduced under the name of Oxophenarsine.

With the successful introduction of several chemotherapeutic drugs, which were mainly used to control protozoal infections attempts were made to control bacterial diseases of man. Working on the line of Ehrlich, Young White, *et al.* in 1920 synthesised mercurochrome, which proved to be a failure. In 1927 Dehme, Leonard *et al* introduced hexylresorcinol but this also was found to be of no value as a systemic anti-infective.

When all attempts to control bacterial infection were unsuccessful and it was thought that sterilisation of the blood stream against some bacterial invasion was an unattainable ideal, Domagk in 1935 made the immortal discovery of Sulphamidochrysoidin which he found will cure an otherwise fatal streptococcus infection in mice. This compound was placed in the market under the name of "prontosil" and it was found that it will differentiate between the protoplasm of the bacteria and that of the man, and will attack the bacteria leaving the tissues of the host more or less uninjured. Since then many compounds have been introduced with wide range of activity and which are less toxic.

Discovery of Penicillin

The introduction of sulpha drugs, which were successfully used as the first chemotherapeutic agents for the treatment of bacterial infection, stimulated Chain and Florey to explore the possibility of purifying Fleming's Penicillin which was discovered in 1928 but could not be utilised in therapy owing to its impure character.

It has been noticed that certain micro-organisms antagonise each other in their struggle for existence. As far back as 1877 Pasteur and Joubert observed that cultures of anthrax bacilli were inhibited by certain air bacilli. This natural antagonism has been termed *antibiosis*. Subsequently Waksmann used the expression "antibiotic" to therapeutic agents responsible for the phenomena of antibiosis. The term antibiotic is now applied to chemical substances produced by micro-organisms, or their growth products, which possess an inhibitory effect on growth and activity of other species of micro-organisms, or destroy infective agents. In 1928 Fleming found that colonies of staphylococcus which were growing on a plate were affected by a colony of mould which developed on this growth and made the epoch making discovery of penicillin.

The fact that certain organisms were not affected by penicillin stimulated search for other antibiotics which will produce effect on organisms which are either penicillin-fast or are uninfluenced by penicillin. While the discovery of penicillin was accidental, that of streptomycin was the result of painstaking research. *Streptomyces griseus* belongs to the group of micro-organisms known as *actinomyces*. Streptomycin possesses a wide range of chemotherapeutic activity, including effectiveness in acute tuberculous infections.

Following the isolation of streptomycin, investigations continued on the production of antibiotics by the actinomycetes, and in 1948 Duggar, working in the Lederle Laboratories Divisions of the American Cyanamid Co., under the direction of the then Director of the Laboratory late Y. Subba Rao, announced the discovery of Aureomycin. Because of its yellow colour which developed in the fungus during its growth and the golden-yellow colour of the antibiotic, the name *Streptomyces aureofaciens* was given to the organism and the antibiotic was called aureomycin.

The discovery of chloromycetin (Chloramphenicol) was first reported in 1947 by a group of workers in the Research Laboratories of Parke Davis & Co. It was obtained from a hitherto unknown species of *Streptomyces* isolated from a sample of soil from a field in Venezuela. A similar organism has been isolated from a compost soil from a farm in Urbana, U.S.A. by a group of workers in the University of Illinois. It is a derivative of nitrobenzene and of dichloracetic acid. As soon as its constitution was established, chloramphenicol was synthesised. In fact it is the first major antibiotic to be synthesised commercially. Interest on this antibiotic also centered on its effectiveness on a group of filter-passing organisms, namely rickettsias.

Of the numerous antibiotics which have been reported from time to time, few have justified their early hopes of their discoveries. The following however deserve special mention. Oxytetracycline (Terramycin) from *streptomyces rimosus*, Erythromycin, Carbomycin and Tetracycline. The readiness with which resistant strains tend to develop, it is a distinct advantage to have so many valuable weapons at our disposal which may be used by rotation.

Chloramphenicol or chloromycetin, aureomycin and terramycin have one property in common and that they can be administered orally and possess similar range of antibacterial activity. They are all effective where both penicillin and streptomycin are useless, namely in Rickettsial infections, virus pneumonia and lymphogranuloma venereum. All are clinically effective in whooping-cough where both penicillin and streptomycin are ineffective. Again chloramphenicol is the only antibiotic which is highly effective in typhoid and paratyphoid fevers. They are all free from grave toxic effect except chloramphenicol which may give rise to aplastic anaemia or agranulocytosis.

Chemotherapy against Malaria

In order to appreciate the problems of chemotherapeutic attack against malaria, it is essential to review the modern conception of the life cycle of the malaria parasite.

What happened to the sporozoites during the incubation period of infection with malaria parasite was till recently a baffling problem. From the experimental

study of *Plasmodium cynomolgi* in the monkey and of *P. vivax* in man, Shortt and Garnham (1948) first demonstrated the existence of a tissue phase of the malaria parasite in the liver.

The sporozoites when introduced into the body soon leave the blood and enter the liver cells as *cryptozoites* where they multiply and start the pre-erythrocytic cycle. The cryptozoites subsequently become cryptomerozoites. After the incubation period cryptomerozoites are released as pre-erythrocytic merozoites, and majority of them enter the red cells as trophozoites, within which they undergo the asexual or erythrocytic cycle of development, which coincides with the clinical attack of malaria. Some cryptomerozoites enter the liver cells and continue their development as secondary exo-erythrocytic cycle. This process may repeat itself indefinitely irrespective of whether the erythrocytic cycle is continuing or held in check either as the result of antimalarial treatment or as the result of naturally acquired immunity. This immunity, however, has probably no effect on the cryptomerozoites in exo-erythrocytic phase, whereas when the immune titre falls due to passage of time, or to disease or devitalisation, these cryptomerozoites commence the erythrocytic cycle in the absence of any fresh infection; in other words the clinical relapse is the result of invasion of the red blood cells by the cryptomerozoites of the exo-erythrocytic phase.

The pre-erythrocytic cycle has been demonstrated in all varieties of human malaria; but exo-erythrocytic forms have not been detected in infection with *P. falciparum*, where relapse is non-existent. They probably die soon after the infection has developed in the blood corpuscles. But in *P. vivax* and *P. malariae* exo-erythrocytic cycle continues indefinitely resulting in frequent relapses which may even occur after very long intervals, 1 to 3 years in benign tertian, even upto 20 years in quartan variety.

Anti-malarial Remedies

Quinine, the first antimalarial agent, used since 1820 still occupies a very important position in the field of therapeutics; and there is no controversy regarding its therapeutic value. Acute shortage of quinine during the Great Wars necessitated the synthesis of a large number of antimalarials, some of which have already established their value in clinical practice. Thus we have pamaquin, mepacrine, proguanil, choloroquine, camoquin, pentaquine, isopentaquine and daraprim.

No drug is yet known which is effective against sporozoites. However complete causal prophylaxis, i.e. destruction of the *P. falciparum* and occasionally of *P. vivax* in the pre-erythrocytic phase can be achieved by biguanides, i.e. proguanil (paludrine) in therapeutic and 8-methoxy-aminoquinolines (pamaquin, pentaquine) in toxic doses. Besides, proguanil although does not kill the gametocytes, renders them incapable of developing in the body of the mosquitoes and thus helps in preventing spread of the disease.

With chloroquine and camoquin there is very prompt clinical response and the parasites disappear from the blood in 1 to 3 days. The chief advantage of camoquin is that a single dose of the drug produces an effective clinical cure.

In spite of the fact that great advances have been made during recent years and new lines of experimental approach for further research have followed the discovery of the exo-erythrocytic forms, the problem of malaria control has not been solved. Since the parasites undergo development in the solid tissue during the incubation period and in the red blood cells during the erythrocytic cycle, it follows that there must be some substance in these situations essential for the metabolism of the parasites. Whether this metabolite is porphyrin, riboflavin, pantothenic acid, or *p*-aminobenzoic acid or some other substance, has not been settled. Real solution of the problem of anti-malarial chemotherapy lies in this direction. Effort should be made to find suitable analogues which will offer competition with the enzyme system for the development of the parasites and thus inhibit their growth. This will be a true causal prophylaxis.

Before leaving the subject of chemotherapy I should mention the contribution that India made in this direction. Emetine, Kurchi and Urea Stibamine deserve special mention. Ipecacuanha in the form of powder was used in the treatment of dysentery but its use was followed by severe nausea and vomiting and it was thought that emetine was responsible for this effect and a preparation known as Pulvis Ipecacuanhae sine Emetinae, i.e. de-emetinised ipecacuanha was introduced. It was Sir Leonard Rogers who first introduced emetine in the treatment of amoebic dysentery and I remember how he was ridiculed at the time by his colleagues. Although kurchi bark was known to be a remedy for dysentery, it was only recently that a complete pharmacological and chemical investigation was made at the School of Tropical Medicine by Col. R. N. Chopra and his collaborators. Last but not least is the outstanding discovery of Sir U. N. Brahmachari of Urea Stibamine in the treatment of leishmaniasis and which has secured the enviable position in the treatment of kala azar.

In India works on antibiotics are being carried on by Prof. S. R. Bose of the R. G. Kar Medical College.

Antiepileptics or Anticonvulsants

Selection of a suitable anticonvulsant for the treatment of epilepsy where it has to be used for a prolonged period without producing any permanent damage to the brain or other vital organs has not been very easy. It is not possible to *cut short* an epileptic attack, one can only prevent attacks or lessen their frequency, the object being to raise the convulsive threshold. Bromides have been used since 1857, but these were discarded not because they were found ineffective but because of the frequent undesirable effects of more or less permanent nature which followed their use, since they had to be used for months or years to keep down the convulsions. Subsequently phenobarbitone replaced to a certain extent bromide. But it depressed not only the motor cortex of the brain but also the sensory area. Next advance was the introduction of methylphenobarbitone or phemitone which was devoid of the hypnotic property of phenobarbitone but was found to be less potent anticonvulsant. Further progress in this direction is the introduction of hydantoin derivatives like phenytoin sodium (dilantin) and methylphenylethylhydantoin (methoin or mesantoin) and troxidone. The hydantoins possess selective depressant effect on the motor area of the cerebral cortex without producing any narcotic effect. They are pre-eminently drugs of choice for the control of psychomotor epilepsy. Troxidone was accidentally discovered by Everett and Richards in 1944 and is effective in petit mal, akinetic myoclonic forms, but is of little value in grand mal. It is not a hydantoin derivative. In this condition it may actually increase the attack or may precipitate status epilepticus.

Anticoagulants

The introduction of anticoagulant drugs is a distinct advance within recent years and they occupy a prominent place in modern therapeutics. Anticoagulants are largely indicated in the treatment of coronary thrombosis and their value depends upon the capacity to prevent further complications such as the spread of thrombosis to adjacent branches of the affected artery, sudden occlusion of a systemic artery, development of pulmonary infarction. In myocardial infarction it checks extension of the clot in the occluded artery and discourages formation of mural clot in the cavity of the heart. It has reduced the mortality rate by 50% in coronary thrombosis. Similarly, its use is of value in postoperative thrombosis and pulmonary embolism.

Of the different anticoagulants, heparin acts when administered intravenously or intramuscularly and is inactive when given by the mouth. It is not by itself an anticoagulant but combines with certain fractions of the plasma proteins which act as an anticoagulant. It inhibits the conversion of prothrombin into thrombin and also interferes with the action of thrombin. It further prevents the agglutination of platelets and thus the liberation of thromboplastin from them. Although heparin acts quickly its effects also disappear quickly so that it has to be administered more frequently, i.e. every four hours to maintain the effect.

The discovery of dicoumarol as an anticoagulant is interesting. Schofield in 1923 described a haemorrhagic disease in cattle as a result of eating spoiled hay from sweet clover. Roderick subsequently showed (1931) that in this disease the plasma prothrombin level was reduced with prolongation of coagulation time. It was found that dicoumarol was the toxic agent. Subsequently it has been synthesised from methyl acetylsalicylate. It is interesting to know that both sodium salicylate and acid acetylsalicylic produce haemorrhage by reducing prothrombin.

Dicoumarol was introduced because of its effect when administered orally. It acts by lowering the prothrombin level of the plasma and also by interfering with the agglutination of platelets and the formation of intravenous thrombi. The effect is similar to that produced by vitamin K deficiency, and it is possible that it acts as a competitive inhibitor of vitamin K since its chemical formula resembles half of dicoumarol molecule.

Its effect is slow takes about 32 to 46 hours and remains active for several days up to one week. Excessive doses may result in haemorrhage. The margin of safety between effective therapeutic doses and toxic dose is very small and it is necessary to estimate the prothrombin time daily which is not always possible. It has therefore been replaced by ethylbiscoumacetate (Tromexan or Pelentan) and phenylindanedione (Dindevan).

Tromexan is more rapid in its action and is cleared more quickly. This is a great advantage over dicoumarol. Phenylindanedione comes midway between the two. Its effect is observed in 24 hours and the peak effect is reached in 36 to 48 hours. It is cleared within 48 hours after stoppage of its use.

Before leaving this subject of anticoagulants it is necessary to mention that there exists two schools. One advocating its use in coronary occlusion and the other condemning its use in this condition. At the meeting of the Royal Society of Medicine in January of this year (1954) two papers were presented with complete opposite conclusions, in favour by A. R. Gilchrist, against by W. Evans. Gilchrist, from observations of 434 consecutive patients claims the mortality rate of the control series 42·2% as compared with 19·5% who received anticoagulant treatment. Thrombo-embolic complications were reduced from 26% to 10%. Evans on the other hand approached the subject mainly from consideration of the published results of himself and other workers. The object of the anticoagulant therapy is primarily to prevent thrombosis within the coronary circulation. In eight investigations on the incidence of thrombosis within the coronary circulation in subjects of cardiac infarction examined at necropsy, comprising 2351 in all, 57% had no coronary thrombosis. He opines that anticoagulant therapy has failed. He further asserts that vitamin K can do little to counteract serious haemorrhages for the damage has already been done before there is a signal for its use. He concludes "It is a sound precept in medicine never to dispense a remedy to a patient when there is doubt that it can do good and when it is known that it can do harm. That anticoagulant treatment in coronary occlusion will go the way of other discarded remedies is certain. Let it go soon, before remorse weighs too heavily on those who may continue for a little time longer to advocate its use."

Haemopoietic System

Pteroylglutamic Acid (Folic Acid) and Cyanocobalamin (Vitamin B_{12}) are the two recent additions for the treatment of macrocytic hyperchromic anaemia. Folic acid however has certain disadvantages. Although the initial response is good and there is prompt reticulocytosis and rapid rise in the red cell count, larger amounts are necessary to prevent relapse in some cases and eventually there may not be any response. Moreover, subacute combined degeneration of the spinal cord does not improve under folic acid, on the other hand this complication may arise during treatment even though there is good haematological response. For these reasons its use is now being discarded in many countries.

Since para-aminobenzoic acid forms part of the molecule of folic acid, it has been observed that administration of sulphadiazine interferes with the synthesis of folic acid from *p*-aminobenzoic acid. It should be noted that folic acid is normally necessary for the formation of granulocytes. This also explains why agranulocytosis occurs in sulphonamide treatment. Conversely folic acid is used in the treatment of agranulocytosis.

With the introduction of liver extract in the treatment of pernicious anaemia many workers both in England and U.S.A. concentrated their attention in finding the liver substance responsible for improvement of this condition. Rickes *et al* in America and Lester Smith in England almost simultaneously (1948) announced isolation of an extremely potent red pigment from liver as small crystalline red needles. It was subsequently found to be identical with a substance required for the growth of the micro-organism, *Lactobacillus lactis* Dorner. It is many thousand times as active as a standard liver preparation. A dose of 3-6 mcg. produced reticulocytes in patients with pernicious anaemia. The role of cobalt in erythropoiesis is difficult to evaluate and its presence in vitamin B_{12} has yet to be assessed. Since the amount of this vitamin from natural sources is very small its commercial production is now being done from the culture liquor of *Streptomyces griseus* as a by-product of streptomycin.

Blood Dyscrasias and Allied Conditions

To this class belong leukaemia or cancer of the blood forming elements, Hodgkin's disease, polycythaemia, etc., and we have now some drugs which are being used but they produce temporary relief. While bacteria can be specifically influenced by certain substances in the body it was thought that it might be possible to influence specifically the metabolism of malignant cells. Little progress however has been made to elucidate exactly how the metabolism of malignant cells differs from other normal neighbours. The mode of action of the different agents used differ considerably. Thus nitrogen mustard is useful in Hodgkin's disease, urethane is effective in leukaemia, etc. It appears therefore that they do not act on a metabolic activity, or enzyme system, peculiar to malignant cells, but rather each of them appear to affect the metabolic function of a particular type of abnormal growth, Aminopterin (folic acid antagonist) acts by blocking the utilisation of folic acid by the nuclear elements of the tissues; mustine (nitrogen mustard) has a specific cytotoxic effect in sublethal doses on proliferative cells. Urethane acts by inhibiting abnormal cellular growth and proliferation. Finally radioactive isotopes which cause destruction of the cellular elements of the various tissues concerned. All these measures are at best palliative, and produce depression of the bone marrow resulting in agranulocytopis, thrombocytopenia, aplastic anaemia, and the like. It is therefore necessary to examine the blood periodically when prolonged treatment is required and also to supplement by transfusion of whole blood.

Radioactive Isotopes

The radioactive isotopes have assumed an important position not only for metabolic studies where its use is now established but also for research and diagnosis.

For experimental purposes they are used to investigate absorption, storage, distribution and clearance of different substances either in the human body or animals. The substance under investigation is "tagged" with a radioactive isotope which acts as a "tracer" since it can be detected in the body by virtue of radiation which it emits. Thus radioactive iron (Fe_{59} prepared by bombarding ordinary iron, i.e., Fe_{58}) has been used as a "tracer" substance to follow its absorption and distribution in the body. Combined with fluorescein, radioactive iodine (I_{131}) has been used to diagnose and localise brain tumours.

Their therapeutic application is confined at present to only four diseases, namely, myeloid leukaemia, polycythaemia vera, functioning matastasis of thyroid carcinoma and thyrotoxicosis. Radioactive phosphorus is used in myeloid leukaemia and polycythaemia vera. It is the treatment of choice in polycythaemia vera. While radioactive iodine (I_{131}) is used in thyrotoxicosis.

To describe in detail about isotopes is beyond the scope of my lecture nor am I competent to discuss. I feel that some elementary idea about isotopes will be helpful to every medical man.

All chemical elements are composed of three essential constituents, namely, protons which carry positive, electrons negative and neutrons no electric charge. Protons and neutrons constitute the nucleus and electrons surround the nucleus. Since neutrons carry no charge and pass through an electric field without deflection they are suitable for bomberding the nuclei of atoms. The mass of protons and neutrons is about the same, i.e., contains one atomic unit each, but that of electron is much less. The atomic weight of an element depends on the total number of protons and neutrons it contains, while its atomic number, hence its chemical properties, depends on the number of peripheral electrons. It follows that the chemical properties of an element will remain unaltered even though its atomic weight is changed. Thus, two or more atoms may have the same chemical properties, the same atomic number but different atomic weights. Different atomic forms of the same element are known as *isotopes*. Since the peripheral electrons are the same, isotopes possess the same chemical properties, but their differences in atomic weight are associated with certain different physical properties. It has therefore been possible to administer an isotope, for example, iron, which can be distinguished physicallv from all other iron in the body, yet which will be mobilised chemically in exactly the same manner as normal iron.

These isotopes are used in millicuries. Thus P_{32} is given in doses of six millicuries. Radioactive iodine (I_{131}) in doses of 1·5 millicuries. One mc. is that amount of radioactive substance of which 37 million atoms disintegrate per second.

Cort:sone and Adrenocorticotrophic Hormone

Although adrenal cortex was known to possess some function and that its deficiency was followed by a condition known as Addison's disease and was used chiefly as a replacement therapy much interest has recently been centred because of its nonspecific uses. Since the adrenocorticotrophic hormone secreted by the anterior pituitary stimulates the secretion of adrenal cortex this hormone popularly known as ACTH is also associated with cortisone. Of the different anterior pituitary hormones ACTH is only used therapeutically.

Several steroids have been isolated from the adrenal cortex. they are :—(1) 11-deoxy-17-hydroxycorticosterone; (2) 17-hydroxycorticosterone; (3) 11-deoxycorticosterone; (4) Corticosterone; (5) 11-dehydro-corticosterone; (6) 11-dehydro-17-hydroxycorticosterone (cortisone or compound E). It has been possible to isolate and identify these substances all of which will prolong life of adrenalectomised animals. Of these compounds 1 and 3 are concerned with the regulation of electrolyte metabolism and water balance; whilst compounds 2, 4, 5 and 6 are concerned entirely with carbohydrate metabolism.

The most important steroids are Deoxycortone also known as metallocorticoid and cortisone also called glucocorticoid. Deoxycortone or DOCA causes retention of sodium and initial loss of potassium, and will maintain life indefinitely in complete absence of adrenals. Cortisone or Kendall's Compound "E" increases the amount of carbohydrate in the body, causes rise of liver glycogen and blood sugar with appearance of glucose in the urine. In addition to these, adrenocortical extracts were used in the treatment of Addison's disease before synthesis of cortisone. Deoxycortone was first successfully synthesised in 1938 and in 1946 cortisone was prepared from deoxycholic acid, normally present in bile.

In 1938 Hench first observed that the symptoms of rheumatoid arthritis underwent a remission during pregnancy or an attack of jaundice. He speculated as to the possible cause and felt that the circulation of some steroid substance in pregnancy and in jaundice might be responsible for this effect. After investigating the activity of several steroidal substances isolated from adrenal cortex, Hench and Kendall (1949) showed that administration of cortisone or compound "E" daily in 100 mg. doses resulted in a dramatic improvement in the general symptoms of rheumatoid arthritis. They further showed that the same results could be obtained by the administration of ACTH. They however observed that interruption of treatment was attended by a rapid return of the symptoms.

Subsequently Klemperer, Pollack and Baehr introduced a series of clinical entities under the name of "collagen diseases." They are rheumatoid arthritis, rheumatic fever, periarteritis nodosa, diffuse scleroderma and serum sickness. According to the new conception all these are considered to be disease of the fibrous connective tissue. The underlying pathological process was found to be a fibrinoid degeneration of collagen. The group of collagen diseases is constantly being added. An alternative name suggested is para-rheumatic disease.

These drugs are being used in scores of diseases with dramatic results in some cases. In fact they have been found very useful in Addison's disease, idiopathic hypoglycaemia, acute rheumatic fever, acute gouty arthritis, status asthmaticus, serum sickness, exfoliative dermatitis and Loeffler's syndrome. They may be of some use in rheumatoid arthritis, psoriasis, disseminated lupus erythematosus, periarteritis nodosa, vasomotor rhinitis, urticaria, ulcerative colitis, etc.

On the other hand they may do positive harm in diabetes mellitus, Cushing's syndrome, hypertension (chiefly ACTH), congestive heart failure and hirsutism. In fact prolonged heavy doses tend to produce characteristic appearance of Cushing's syndrome, i.e., moon face, plethora, cervical and supercervical pads, abdominal striae; but these are reversible on cessation of therapy. Continued use may lead to hyperglycaemia and glycosuria, disordered mental and sexual functions and retention of sodium and depletion of potassium, leading to oedema, hypertension and heart failure.

In a recent investigation on the use of cortisone and ACTH in the treatment of ulcerative colitis, Truelove and Witts on cortisone and Dick and Beckett on ACTH give detailed account of the results of their observation.

Truelove and Witt's observations are based on 210 cases of which 109 were treated with cortisone, the usual dose being 100 mg. daily for six weeks, while 101 cases acted as control. They hold that cortisone exerts a beneficial influence on the outcome of an acute attack of ulcerative colitis. Dick and Beckett used ACTH and assert that it has a definite place in acute and severe cases of recent onset. On the other hand massive haemorrhage, perforation and peritonitis have been reported by others.

It has been suggested that periodic use of cortisone might prevent adrenal exhaustion during ACTH therapy, while prolonged use of cortisone may depress endogenous

ACTH production, a process which may be reversed by alternating ACTH with cortisone.

Although ACTH is used in place of cortisone and produces almost the same effects, its administration stimulates the release of several steroids. On the other hand it is less reliable since its effect depends upon the functional integrity of the adrenal cortex, whereas cortisone can act, even in the absence of the gland.

Recent biochemical studies suggest that salicylates and aspirin also act by endogenous liberation of ACTH. In this connection the conclusions of the American Heart Association are of interest "there is scarcely a difference between the principal action of ACTH and aspirin because both these substances use the same physiological mechanism". And the American physicians have called cortisone a "glorified aspirin" at least for the treatment of rheumatic fever or rheumatoid arthritis.

Antihistamines or Histamine Antagonists

Histamine, though widely distributed in the animal tissue, is physiologically inactive, possibly because it exists in some bound form and is released only as part of the response of tissues to a variety of injurious stimuli, both physical and chemical. Once liberated it produces variety of effects on the central nervous system, autonomic nervous system and the tissues under their control, such as smooth and skeletal muscles, heart, vessels and secretory glands. Unlike adrenaline and acetylcholine, which are also liberated in the body, none of the normal activity of the tissues are controlled by histamine, yet a very small dose, either injected or scratched into the skin will produce most striking changes and these changes vary in different species of animals.

In 1910 Dale and Laidlaw first pointed out close resemblance of histamine effect and anaphylactic shock. And it is now recognised that the peculiar response is the result of combination of specific antigen with antibodies attached to fixed tissue cells. Dale in 1948 attributed the variation of symptoms in different animal species as being due to difference in distribution of the sensitising antibody. It has further been suggested that the complex symptoms of anaphylaxis may not be due to histamine alone but also to other substances like acetylcholine, heparin, etc., and this is generally spoken as H-substance which is released from the bound inactive state by the action of the injurious stimuli.

As mentioned before histamine normally present in the body remains in an inactive form and it is customary to describe the changes in allergic reaction as being due to "release" of histamine which may affect the cells themselves which release it, or some remote parts of the body may be affected. Dale describes the former effect as the *intrinsic* and the latter effect as the *extrinsic action*. Antihistamine drugs are expected to act more readily against the extrinsic than against intrinsic histamine so that they are more effective in urticaria and vasomotor rhinitis than in spasmodic asthma, due possibly to difference in the site of release of histamine.

Many attempts have been made to antagonise histamine effect, i.e. H-substance and to give relief to sufferers from allergic reactions. Since sympathomimetic amines counteract some of the symptoms of anaphylaxis, adrenaline and ephedrine were used, as also atropine, because of its anti-acetylcholine action. They are classed as *physiological antagonists*.

It was soon realised that these drugs possess other important actions of their own which were not always desirable. Search was therefore made to find compounds possessing specific antihistamine effect, i.e. will act as histamine antagonists without producing any direct antagonistic pharmacological actions. These are classed as *competitive antagonists*.

Bovet and his co-workers first observed that phenolic ether (929F) possessed definite anti-histamine actions, but it was too toxic for therapeutic use. This however acted as an impetus and quite a large number of compounds of varying potency and toxicity were produced by modifications of its chemical structure. It has been found that most of the antihistamines are derivatives of ethylenediamine. Finally, anthisan or mepyramine was discovered which was found to be a very active and specific compound.

Since histamine is destroyed by enzyme histaminase, and that this destruction occurs in the body, Torantil, a preparation of histaminase, was introduced for the treatment of conditions believed to be due to histamine. When administered by the mouth this albuminous material was destroyed and there was no evidence that it destroyed histamine when used by injection. Attempt was made to prevent release of H-substance or histamine by inhibiting histidine decarboxylase, e.g. by the use of rutin, or desensitise the tissues to histamine by repeated use of small doses of histamine itself.

True antihistaminic drugs with which we are concerned act by blocking the action of histamine by competitive action at the cell receptors without possessing any direct antagonistic effects. Broadly their principal actions are more or less the same and for practical purposes they may be divided into three groups :—

1. *Very potent and highly sedative* : Diphenhydramine hydrochloride (benadryl), promethazine hydrochloride (phenergan). Phenergan is the most powerful and produces maximum effect at four to twenty hours after oral use.

2. *Potent and moderately sedative* : Mepyramine maleate (anthisan), tripelennamine (pyribenzamine). These are powerful and long acting but not as promethazine.

3. *Less potent and no sedative action* : Phenindamine (thephorin, antistin). Thephorin on the other hand, has a stimulant action.

Contrary to the usual belief, most of these drugs produce certain side-effects, some more others less. They are as follows :—

1. *Central nervous system.*—They produce drowsiness and central analgesic effect. Some produce this with ordinary effective doses while with others it is rare. It is better not to allow a person taking these drugs to drive a car or do responsible work.

2. *Local anaesthetic effect.*—This property is marked with all but some like mepyramine maleate is three times more powerful than procaine. It is possible that the good effect may have something to do with this property.

3. *Quinidine-like action on the heart.*—They prolong the refractory period of the heart, specially mepyramine.

4. *Anti-acetylcholine action.*—They produce dryness of the mouth and counteract the effect on smooth muscle including muscles of the vessels. In other words they possess atropine like action.

An ideal histamine antagonist has yet to be produced. A drug which will produce maximum antihistamine effect with minimum side-effects, has yet to be found.

NOTES AND NEWS

International Congress of Biochemistry

The 3rd International Congress of Biochemistry organised by the Société Belge De Biochimie, under the auspices of the International Union of Biochemistry will be held at Brussels on 1-6 August, 1955. Detailed information may be had from the General Secretary, 17, place Delcour, Liège (Belgique).

Inventory of Teaching Equipment for Medical Schools

A detailed inventory of the equipment needed to set up a medical school is now available as the result of a joint undertaking by the WHO and UNESCO.

This important reference manual is intended chiefly for use in new medical schools but is also expected to be of help to existing medical schools which plan to reorganize their teaching departments on more modern lines.

This is Part V, "Medical Sciences", of Volume III, of the UNESCO series "Inventories of Apparatus and Materials for Teaching Science". The World Health Organization has been responsible for the preparation of the manuscript and for the entire technical presentation, while the publication and translation have been the responsibility of UNESCO.

The book contains lists of equipment used in instruction of medical students in 8 subjects: (1) Anatomy, (2) Bacteriology (microbiology), (3) Biochemistry, (4) Histology, (5) Morbid Anatomy (Pathology), (6) Pharmacology, (7) Physiology and (8) Preventive and Social Medicine (hygiene and public health).

Uttar Pradesh to Fight Tuberculosis

The U. P. Government has allotted a sum of Rs. 67,400 for providing 76 additional T. B. beds in Ferozabad Combined Hospital. A 26-bed T. B. hospital was opened there last year.

The State Government has also decided to provide 300 additional beds for teachers and students suffering from T. B. and a sum of Rs. 15 lakhs has been allotted for this purpose. The Government recently opened a 50-bed sanatorium at Gethia (Naini Tal) for them.

A sum of Rs. 13,000 has been granted for starting a surgical unit at Ferozabad for conducting major operations in T. B. for which a well-equipped operation theatre is being constructed.

Madras Medical Council

On the information received by the Registrar, Madras Medical Council, that Dr. C. Oommen, L.M. & S., is issuing certificates to the candidates trained by him as Chairman of the Board of the Grace Medical Mission, Navelikara, and associating with unqualified persons and thereby transgressed the Code of Medical Ethics, the Madras Medical Council held an enquiry and at the meeting held on 18th October 1954 found him guilty of infamous conduct in a professional respect and in exercise of the powers conferred on it by section 16(2) of the Madras Medical Registration Act, 1914 (Act IV of 1914), directed that the name of Dr. Oommen Chochandy, L.M. & S. (Madras), 1917, holder of Registration Certificate No. 1580, dated 1st November 1917, be erased from the Madras Medical Register for a period of five years.

Minto Medal Award

Dr. R. N. Chaudhuri, Director, School of Tropical Medicine, Calcutta, who was adjudged to be the best worker in the field of medical research, done in India in 1954, has been awarded the Earl of Minto Medal.

His notable contributions are on chemotherapeutic control of malaria and protection of epidemic dropsy ascites in monkey, rat and rabbit.

Previous recipients of this medal were among others Sir Upendra Nath Brahmachari, Sir Ram Nath Chopra, Lt.-Col. S. S. Sokhey, Lt.-Col. C. L. Pasricha, Dr. C. G. Pandit, Dr. K. V. Krishnan and Dr. D. N. Roy.

Salaries to Professors of non-Clinical Subjects

The Union Health Minister in laying the foundation-stone of an operation theatre and two wards in the Bhopal Government Hamidia Hospital said that her Ministry had submitted a scheme to the Planning Commission, envisaging grants of Central subsidy to the State Governments for paying reasonable salaries to professors of non-clinical subjects in medical colleges.

The subsidy, she said, was proposed to be continued till such time as the State Governments were able to tap local sources to meet the increased burden of expenditure.

This scheme would encourage young men to join the profession and thus relieve the acute dearth of professors on non-clinical subjects in the country, she added.

She also said it had been decided to form an all-India cadre of service for professors of non-clinical subjects to stabilize their working conditions.

Dr. S. C. Sen on Voluntary Health Insurance

Dr. S. C. Sen, President of the Indian Medical Association who was addressing the Dehra Dun Branch of the Association on February 12, 1955, suggested that a voluntary insurance scheme for medical purposes should be introduced in India to improve national health and said that middle class families with income from two hundred to three hundred rupees a month should entrust themselves to the care of a doctor and pay him two to three per cent of their income as cover against all medical needs, including the cost of medicine. The doctor should pay frequent visits to the families, periodically check up and regulate dieting. The poorer people, he said, should be treated in the State and charitable hospitals.

Dr. Sen said that he did not favour socialisation of medicine now as the Government pattern and financial resources in India did not suit such a collective measure. He appealed to the doctors to work honestly and observe medical ethics in relation to society and patients with the dignity and honour of the profession.

Fleming Passes Away

Sir Alexander Fleming, the discoverer of Penicillin and Nobel Prize winner, died at his home on 11 March 1955. He was 73.

Sir Alexander was born in 1881, the son of a Scottish farmer. A brilliant schoolboy, whose early career was a record of scholarships and gold medals, he eventually became a teacher at London University. There he was assistant to Sir Almroth Wright, the father of modern vaccine therapy. He contributed to the research which produced World War II's first wonder drug, M & B 693, and it was he who discovered that tears contain an antiseptic substance called lysozyme, a discovery of great physiological importance.

It was his work as an army doctor in World War I that set him thinking on the lines that eventually led him to his great discovery of Penicillin.

In 1914 he was knighted for his great service to science and the cause of humanity and in 1945 he received the Nobel Prize for Medicine. He was awarded the French Legion of Honour and was made a member of the Academies of Medicine in Paris and Rome and a member of Britain's Medical Research Council.

He was the author of numerous publications on bacteriology, immunology and chemotherapy.

In December, 1950, he was elected an honorary Fellow of the National Institute of Sciences in India.

CORRESPONDENCE

The Editor is not responsible for any views expressed by correspondents

General Practitioners in the Control of Tuberculosis

SIR,—The gravity of the problem of tuberculosis and its effect on the immediate and future socio-economic life of our nation has been amply discussed in the medical and lay press by eminent leaders and social workers. Amongst various suggestions, much importance has been attached to co-operation by general practitioners. It is gratifying to note that Major K. N. Rao (Golden Jubilee issue of Antiseptic) has tried to bring the question to the forefront and further enlightening discussions will not be superfluous. A bold and true orientation is necessary.

Major Rao has rightly stressed on this as the first step and he has also given us an idea of the extent of the disease in the State of Madras. But it must be admitted that no real, genuine and scientific attempt has been made to get a census of the affected persons in the majority of the States and no light has been thrown till now how the general practitioners may co-operate in obtaining such an evaluation. On the other hand there is sufficient reason to apprehend that the State Governments are not going to undertake any tuberculosis census. Individual specialists, social workers and benevolent societies are too much biassed on personal guesswork and not worth the name of scientific evaluation.

The medical practitioner is the most valuable link in any effective national health programme; but in our country how this link is going to be established nobody knows. Till now no plan has been formulated about campaign against tuberculosis utilising the vast number of general practitioners. On the contrary he is given the least importance in both prevention and relief.

About specific measures, B.C.G. vaccination and isolation of cases should both be considered. Attempt under the WHO for BCG Vaccination is a noteworthy step but not successful as an all-round programme. Instead of mobile batches of short-trained non-medical men under a medical supervisor who are playing their part admirably but working on an itinerant camp basis are leaving unexplored pockets behind their hasty tours, it would have been a bold and nation-wide step to appeal to the general practitioners in all corners of the country to take the necessary training and carry on the work permanently and continuously. About the isolation of cases, the less said the better—almost in every village, a few latent and a few open cases are continuously spreading the infections to their neighbours who are callous and helpless in isolating them and the general practitioners have nothing to do except consoling the public with empty sympathy and gratis advice.

Domiciliary care and treatment discussed by Major Rao affords the most practical solution for the cases requiring immediate relief and rehabilitation. The problem lies not so much in the selection of the type of treatment as on the way how the selected treatment will be brought home to the patient and how the co-operation of the general practitioners may be utilised for success of the treatment selected in consultation with the specialist.

The general practitioners do try to take lively interest in these campaigns and in their day to day practice try to dispel the ignorance of the public. Many of them take active part in the sale of T.B. seals and raising other social service funds but are discouraged by the public who have faith only in immediate realistic benefits occurring to the rural masses.

When the general practitioner finds that he can take greater share in the treatment of this disease, he will be inspired to undergo refresher courses, otherwise his knowledge of recent advances will be nothing but flying from various "inns" to various "Mycuis". I am etc.

Garhbeta,
Midnapore. K. P. DE, M.B.

Employees' State Insurance Scheme, Bombay

With reference to the letter of Dr. Chimanlal O. Sanghavi with the above heading published in the December 16 issue of the Journal, the following correspondence passed between the Medical Commissioner, E.S.I.C., Ministry of Labour, New Delhi and Dr. Sanghavi of Bombay.—ED., *J. Indian M. A.*

Copy of letter from Medical Commissioner, E.S.I.C., dated New Delhi, 4th March, 1955, to Dr. Chimanlal O. Sanghavi.

My attention has been drawn to your letter which appeared on page 233 of the Journal of the Indian Medical Association, Volume 24, dated 16th December, 1954, wherein it is stated that the attendance of the insured persons in your clinic was 8 to 9 per cent. You have also desired that some one may suggest as to how to check this high sickness rate as well as to check the increasing number of certificates which are demanded under the wrong pretext by the insured persons. I have since made necessary enquiries and indicate certain particulars in this respect in the form of a table.

Month	No. of insured persons on list.	No. of insured persons attended to.			Percentage of daily attendance	No. of certificates issued.			
		New	Old	Total		First	First & Final	Intermediate	Final
Nov. ...	300	100	245	351	3·9	35	nil	4	8
Dec. ...	330	79	153	232	2·3	22	nil	1	7
Jan. ...	300	140	178	318	3·0	12	10	1	4
Feb. (till 15th)	300	72	120	192	3·6	5	12	10	4

It may be seen from the above statement that the percentage of daily attendance varied between 2·3 to 3·9 and that the number of medical certificates issued during the period was about 1·2 certificates per day. The insured persons who needed immediate medical attention got themselves registered with a panel doctor and the final selection of doctors by insured persons was obviously spread over some period of time. The position seems to have stabilised to some extent and this is the basis on which our calculations are generally based, and, therefore, it calls for no action.

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Copy of letter from Dr. Chimanlal O. Sanghavi to the Medical Commissioner, E.S.I.C., New Delhi.

I am in receipt of your letter dated 4th March, 1955, in connection of my article which appeared on page 233 of the Journal of the Indian Medical Association, Vol. 24, dated the 16th December, 1954.

The letter in question, though published on 16th December 1954, was sent for publication in November 1954, in view of the sickness percentage in the month of October 1954, when the scheme had just started.

I do agree that the scheme has stabilised by now, but those were the days when an insured person used to come with an Identity Slip in one hand and a bottle for medicine in the other.

As regards 8 to 9 per cent of sickness referred to in my letter I shall give statistics of one of the sample week beginning from Monday, 11th October 1954.

Date Oct. 1954	No. of Insd. persons on list.	Total No. of Insd. persons attended to	Percentage of daily attendance.
Mon. 11th	63	6	9
Tue. 12th	77	8	10·4
Wed. 13th	87	10	11·5
Thu. 14th	96	8	8·3
Fri. 15th	109	4	3·6
Sat. 16th	120	8	7

During the week average percentage of daily attendance was 8·3.

I am awfully sorry for the inconveniences caused to your good office by my article, but the above statistics prevailing at that time justify the same.

REVIEWS

Review of Medical Microbiology—By E. Jawetz, J. L. Melnick and E. A. Adelberg. Lange Medical Publications, California, U.S.A., 1954, pp. 390. Price $4.50. Sole Distributors in India—The Kothari Book Depot, Bombay.

Written in a concise, class-note dictation style, this book contains the information which the students of medicine should know. However, those who would like to take up bacteriology as a career would perhaps like to know more details about technique, and about the developments and controversies which have maintained the continued advance of bacteriology—medical or otherwise applied. And the authors have given a list of books and journals to help such studies. The book, which is lithographed, is well illustrated.

The Haemolytic Anaemias—Congenital and Acquired.—By J. V. Dacie, M.D., M.R.C.P. Published by J. & A. Churchill Ltd., 104 Gloucester Place, London, W. 1. Price 50 sh. net.

The book contains a comprehensive and up-to-date account of haemolytic anaemias critically studied from various angles. The first chapter deals with the common manifestations of haemolytic process as also the general investigative procedures. Then follow the five chapters on congenital haemolytic anaemia and six chapters on acquired haemolytic anaemia of auto-immune type. Subsequent chapters deal with secondary haemolytic anaemias, paroxysmal nocturnal haemoglobinuria and haemolytic disease of the newborn. The last chapter contains the laboratory methods used by the author in the study of haemolytic diseases.

Written by a pioneer research worker who has richly contributed to the immunological aspects of haematology, the book may be rightly regarded as an authoritative monograph on the subject. The chapters on the acquired haemolytic anaemia, particularly the serological aspects of the disease, are remarkably well written. Different aspects of the important diseases have been clearly illustrated by the case histories of a series of cases personally studied by the author. The clinical and therapeutic aspects of the haemolytic diseases have also received due emphasis. In the pages of the book will be found all the current methods of therapy. The extensive bibliography at the end of each chapter is remarkably up-to-date.

As stated by the author the laboratory methods in the last chapter include only those used by the author; these are no doubt standard methods which are widely followed. The reviewer, however, feels that in keeping with the comprehensive and exhaustive standard maintained in the preceding chapters there is some scope of expansion of the chapter on methodology.

On the whole, the book is a valuable contribution and will be welcome by all interested in the subject.

Handbook of Medical Treatment —Pp. 509. Fourth Edition, 1954. Lange Medical Publication, Los Altos, California. $3·00.

This handy volume of the 4th edition of Handbook of Medical Treatment is sure to be accepted well by the medical profession like the previous editions. Though the present size of the book has been considerably expanded still it remains a comfortable volume for ready and rapid reference.

There are 22 chapters with an appendix covering practically most of the important aspects of medicine. The chapters dealing with fluid balance and shock will be of great value to practitioners in general. Most of the other chapters written in a small space carry very useful and the more recent information. This handbook can be strongly recommended as a book for ready reference in medical management to every member of the medical profession.

SUPPLEMENT

Journal of the Indian Medical Association

VOL. 24, No. 13 CALCUTTA APRIL 1, 1955

BRANCH NOTES

BANGALORE BRANCH—On 4-9-54 the Annual General Body Meeting of the Association was held. Dr. C. V. Natarajan presided. 64 members were present. Office-bearers were elected for 1954-55 with Dr. M. Sirsi as president and Drs. M. Guru Das and P. T. A. Chette as secretaries. The secretaries' report and the audited accounts were approved.

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On 5-9-54 a party of about 50 members went to Thippagondanahalli in connection with the Annual Day. After enjoying variety entertainments and indoor games, all returned to Bangalore in the evening.

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On 25-9-54 Dr. M. N. Mahadevan addressed the Association on Pulmonary Heart Disease. Dr. Sampath Loganathan presided. More than 60 members were present.

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On 9-10-54 a meeting of the Executive Committee was held at 4 P.M. Dr. M. Sirsi presided. It was resolved to request all the members to enrol one or more members to the Association. It was also decided to send Dr. M. Guru Das to represent the Association in the Telephone Advisory Committee.

Dr. S. C. Kuppanna delivered a lecture on Diagnostic Trend in Congenital Heart Diseases, with Films. 45 members were present.

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On 13-11-54 Dr. M. R. Goverdhan delivered a lecture on "The Role of Medical Profession in Public Health". Dr. M. Sivaram presided. 46 members attended the meeting.

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On 18-11-54 Dr. Katherine Kuder addressed the Association and screened the Film 'Studies in Human Fertility', under the presidentship of Dr. Ratnamma Issac. 55 members were present.

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On 11-12-54 Dr. M. Sivaram gave a lecture on "Ephebiatrics and the General Practitioner". Dr. M. V. Govindaswamy presided. 55 members attended the meeting.

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On 17-12-54 Dr. B. Ananthaswamy Rao delivered a lecture on "Impressions of Medical and Public Health Conference". Dr. S. R. Bhombore presided. 50 members were present.

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On 18-12-54 a meeting of the Working Committee was held. Dr. M. Sirsi presided. It was decided to send a questionnaire to all the members for ascertaining facts to strengthen the Association.

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A meeting of the branch was held on 29-12-54 with Dr. J. C. Sharma in the chair. Dr. D. R. Sharma the secretary was authorised to protest against the realisation of Rs. 5/- per annum as licence by the local authorities and the undignified behaviour shown to the members of the medical profession. The byelaws were adopted.

A meeting was held on 9-1-55 to condole the death of Dr. S. Subba Rao, a former president of Mysore Medical Association and Dr. B. Chokkanna, a member of the branch. Dr. M. Sirsi presided.

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A Working Committee meeting was held on 14-1-55 with Dr. M. Sirsi in the chair. Dr. E. Rothlin spoke on 'Rational Health Therapy'.

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On 17-1-55 Drs. J. R. Rees and F. F. Smith of World Health Federation for Mental Health gave a lecture. On 22-1-55 Dr. S. C. Sen, president, I.M.A., gave a talk on 'Some Problems of Medical Profession'. Dr. M. Sirsi presided.

BEGUSARAI BRANCH—A meeting of the branch was held on 6-12-54 with Dr. K. P. Singh in the chair. Eleven members were present. Dr. S. N. Imam asked the house as what could be the cause of Acute Unilateral Non-inflammatory Swelling of one leg of a patient who was being treated in his ward.

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A meeting of the branch was held on 7-1-55. Dr. H. K. Sinha presided. Thirteen members were present. Dr. Akhter Saheb agreed to give a plot of land for the Association building. Dr. Mullick narrated a rare complication of measles. Dr. Gupta gave a talk on Ayurvedic principles.

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An extraordinary meeting of the branch was held on 27-1-55. Fifteen members were present. Dr. K. P. Singh was in the chair. Celebrations of Bihar Health week was decided upon. It was decided to form a health week sub-committee.

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A meeting of the branch was held on 7-2-55 with Dr. H. K. Sinha in the chair. Twelve members were present. Dr. M. N. Sinha was appointed secretary of the Health Week Sub-committee. It was decided to immediately register the land for the building of the association. Members were requested to donate Rs. 25/- each to the building Fund. It was decided to approach the pharmacists also in this connection.

CALCUTTA BRANCH—A meeting of the Executive Committee of the branch was held on 20-12-54. Dr. N. K. Munshi presided. Twentysix members were present. Seventy-four new members were enlisted. The procedures for holding the 14th Bengal Provincial Medical Conference were discussed. Regarding the lecture of Prof. Dr. Ernest Rothlin on "Rational Heart Therapy" the house directed for communication to the speaker that proprietory products should not be referred to in the lecture.

CHAPRA BRANCH—A meeting of the branch was held on 3-1-55 to record its sense of sorrow at the sad death of Dr. Bejoy Chandra Gupta, an active member of the branch.

CHINGLEPUT DISTRICT BRANCH—A meeting of the general body was held on 13-11-54. Dr. P. S. Sreenivasan presided. Office-bearers for 1954-55 were elected with Dr. P. S. Sreenivasan as president and Dr. R. Varadarajan as secretary. The statement of accounts for 1953-54 was approved. Dr. K. Narayanamurthy spoke on "Treatment of Amoebiasis".

CHIRALA BRANCH—The inaugural function was held on 27-10-54 with Dr. K. Sadasiva Rao of Guntur as president. Dr. D. J. Reddy, principal of Guntur Medical College in delivering the inaugural address stressed the need of an organisation of practitioners of modern medicine. He also gave a talk on "Cirrhosis of the Liver".

DALTONGANJ BRANCH—A special meeting of the branch was held on 12-12-54 under the presidentship of Dr. S. A. Mozaffar. A large number of members including those from the Mofassil attended. The meeting was addressed by Dr. P. N. Sinha, Professor of Clinical Ophthalmology, Patna Medical College who gave his impressions of his tour of foreign countries recently concluded with special reference to the problems of important eye-diseases in different countries and the ways in which they were being tackled.

DAVANGERE BRANCH—The annual meeting of the branch was held on 14-9-54 with Dr. K. S. Shadakshareppe in the chair. Dr. B. I. Gopal Rao was elected the president for the next year and Dr. Y. A. Narayana the secretary.

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At the monthly meeting held on 6-11-54 with Dr. S. N. Dhananjay in the chair. Dr. M. R. Shiva Shankarappe spoke on "Emergencies in Dental Practice".

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At a special meeting held on 7-11-54, Dr. Shannavammal of Bangalore spoke of Tuberculosis of Caecum".

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At the monthly meeting held on 11-12-54, Dr. H. K. Krishnaswamy presided and Dr. S. R. Medvachav a hearty send-off to Chikmagalur.

DEORIA BRANCH—A general meeting of the branch was held on 12-12-54. Dr. S. C. Acharya presided. Ten members were present. Dr. J. P. Mathur demonstrated a case of Prolonged Pyrexia with Ascites. Dr. B. P. Mohindra described a case of Tuberculosis which developed from Pott's Disease and later to Miliary (generalised) in course of 8 years.

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A meeting of the branch was held on 23-1-55 with Dr. S. C. Acharya in the chair. Ten members were present. To control incidence of dog bites, it was considered essential that stray dogs should be killed. The members placed on records their appreciation of the presidential address of Dr. S. C. Sen at Lucknow.

DHANBAD DIVISIONAL BRANCH—A meeting of the branch was held. More than 100 doctors of Dhanbad sub-division joined the meeting and the picnic following.

GARBETA BRANCH—The annual general meeting of the branch was held on 16-1-55, with Dr. J. B. Ghose in the chair. Thirteen members were present. Office-bearers for the year 1954-55 were elected with Dr. J. B. Ghose as president and Dr. K. P. De as hony. secretary. The notable activities of the past year were, (1) The branch organised public meetings to start a co-operative Polyclinic and to prevent sale of spurious drugs (2) A memorandum was submitted by all parties for antiepidemic measures and supply of pure drinking water (3) A signature campaign for the improvement of the thana Health Centre was launched (4) A flood relief fund was raised and forwarded to the Provincial Branch.

GURGAON BRANCH—The annual report of the branch for 1953-54 shows that 13 members were held during the year. There was a fall in membership. The financial position is satisfactory. In the meetings held during the year interesting clinical subjects were discussed.

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The annual meeting of the branch was held on 9-1-55. Dr. Singh presided. Thirty-one doctors were present. The annual report was adopted. Office-bearers for 1955 were elected with Dr. S. Singh as president and Dr. D. P. Puri as secretary. Dr. B. R. Puri spoke on 'Poliomylitis'. Dr. H. B. Dingley of R. S. Tuberculosis Hospital spoke on Tuberculosis.

FAIZABAD BRANCH—A meeting of the branch was held on 8-1-55. Dr. S. S. Misra presided. Dr. L. N. Saxena gave a talk on "Pathogenesis of Tuberculosis".

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A meeting of the branch was held on 22-1-55 to bid farewell to Dr. V. S. Srivastava, on transfer to Lucknow.

JAGATDAL BRANCH—A meeting of the branch was held on 1-2-55 with Dr. S. C. Bhattacharyee in the chair. Thirty members were present. Dr. J. N. Moitra gave a report on the All India Medical Conference at Lucknow. A memorandum by the Industrial Medical Officers of the branch regarding their position in relation to E. S. I. S. was discussed and approved.

JALPAIGURI BRANCH—The North Bengal Medical Conference was held on 3-7-54 with Dr. C. Sanyal as president. Dr. Sanyal in his address referred to Tuberculosis and Leprosy which are spreading rapidly in the area. He suggested the starting of a botanical garden in the area to make researches on the medicine plants which are abundant there. He also wanted to approach the Government for the establishment of a medical college in that area.

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The annual general meeting of the branch was held on 9-1-55. Nineteen members were present. Dr. A. D. Guha Neogy presided. Office-bearers were elected with Dr. A. Guha Neogy as the president and Dr. S. C. Bhowmik as hony. secretary. The annual report and the audited accounts were adopted. The annual report of 1953-54 shows that 9 meetings were held during the year. There was no increase in membership.

JAMBUSAR BRANCH—A meeting of the branch was held on 14-11-54. Dr. J. M. Shah was in the chair. Dr. C. C. Jambusaria discussed "Convulsions in Infants".

JORHAT BRANCH—The annual general meeting of the branch was held on 15-1-55. Dr. R. M. Deb was in the chair. The secretary's report and the accounts were adopted. Office bearers were elected with Dr. R. M. Deb as president and Dr. A. K. Roy as hony. secretary.

HASSAN BRANCH—A meeting of the branch was held on 12-2-55. Dr. M. Monoraj presided. The members condoled the sudden death of Dr. S. Subba Rao. Dr. H. V. Surjanarayana Rao spoke on E.N.T. diseases in general. Dr. K. Narasinha presented a case report of Lymphatic Leukemia. Twenty-eight members were present.

KANDI BRANCH—A meeting of the branch was held on 9-1-55. Dr. B. P. Ghosh Hazra presided. Thirteen members were present. Major S. Ghosh spoke on "Blood Transfusion".

KALYANI BRANCH—The annual general meeting of the branch was held on 24-12-54 with Dr. S. K. Ganguli in the chair. Office bearers for 1954-55 were elected with Dr. S. K. Ganguli as president and Dr. A. R. Dutt as secretary.

KUTCH PROVINCIAL BRANCH—The annual meeting of the branch was held on 7-11-54. Dr. M. M. Dalal presided. Seventeen members were present. Dr. S. S. Dhru, Dr. V. P. Dandekar, Dr. S. V. Sathe read papers on Tetanus, Pulmonary Eosinophilia and Hospital Administration respectively. Consideration of the question of amalgamating Kutch Provincial Branch with Gujarat and Saurashtra Provincial Branch was postponed. Office bearers for 1954-55 were elected with Dr. H. J. Chauhan as Secretary.

KURNOOL BRANCH—The annual meeting of the branch was held on 31-10-54. The following members spoke on the following subjects: Dr. K. Rajamannar on Common Daily Surgical Emergencies, Dr. G. Balasubbajah on Recent Advances in the Treatment of Venereal

Diseases, Dr. C. T. Tilak on Surgical Treatment of Portal Cirrhosis and Dr. P. Seevaiah on Guinea Worm Infection.

LABAC BRANCH—A meeting of the branch was held on 26-9-54. Dr. S. C. Ghosh was in the chair. Ten members were present. Dr. S. C. Ghosh was elected the president of the branch for 1954-55 and Dr. A. Das, the hony. secretary.

MADRAS STATE BRANCH—A meeting of the Council of the branch was held on 20-11-54. Dr. V. P. Vasudevan presided. Forty-six members were present. The members condoled the death of (1) Dr. V. S. Kesavan, Coimbatore and (2) Dr. K. N. Kini, Bangalore. The secretary informed the House that the Madras City Branch has agreed to arrange a meeting at Madras while the two members of the United States Committee of W. M. A. are at Madras. The names of doctors recommended for internships were announced. Amendments passed previously have been incorporated in the Rules and have come into force from 1-10-54. The annual report for 1953-54 and the audited report were adopted. Dr. R. Sankaran was re-elected hony. secretary for 1954-55. Members for the Working Committee were elected. The Council approved Dr. R. Kalamegham's undertaking to edit "The Miscellany". It was decided to request the Government to exempt medical men owning X'ray plants from paying the license fees. The hony. secretary was asked to request the Government to convert the present quarterly "Medical Bulletin" into a regular medical Journal for the benefit of the medical profession.

MADRAS BRANCH—The annual general body meeting of the branch was held on 2-12-54 with Dr. P. Natesan in the chair. Ninty-five members were present. The annual report and the accounts for the year ending 30-9-54 were adopted. Office bearers were elected with Dr. Santhosham as president and Dr. V. Vijayaraghaban and Dr. W. Sridhara as hony. secretaries. The changing of the name of Madras Branch to Madras City Branch was adopted. The annual report of the branch for 1953-54 shows a fall in membership. During the year 6 lectures were held on interesting subjects. Nine executive meetings and 3 general body meetings were also held. The South Indian Medical Union being wound up, the assets of the Union amounting to Rs. 1,124-0-9 were transferred to this branch.

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A meeting of the branch was held on 18-12-54. Dr. A. S. Annamalai was in the chair. Fifty-eight members were present. Dr. T. V. Venkatesan spoke on "Some Recent Drugs and their Clinical uses."

MAHBOOBNAGAR BRANCH—A joint meeting of Nalgonda and the Mahboobnagar branch was held on 19-12-54. Dr. F. Hussain presided. Eighteen members were present. Dr. J. J. Reddy presented a case of "Mitral Stenosis". Later Dr. H. C. Khanna read a paper on "Cardiac Asthma". He also described "Scarlet Fever" and how recurrent epistexis and sore throat lead to Rheumatism and Rheumatic Chorea.

MALABAR BRANCH—A meeting of the branch was held on 18-12-54. Dr. P. B. Menon presided. Dr. M. K. Mohamed Koya, the secretary was authorised to issue a press statement regarding B.C.G. vaccination and to request the public of Calicut to give full co-operation to the scheme. Dr. P. K. Krishnan Kutty spoke on "Cardiac Emergencies in General Practice."

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A special meeting of the branch was held on 25-12-54. Fifty members were present. Dr. Adi Subramaniam, Director of Public Health, Madras, addressed the members on B.C.G. Vaccination.

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A meeting of the branch was held on 28-1-55. Seventy doctors from Calicut and muffasil attended. Lt. Col. Sanghan Lall, Director of Health Services, Madras, who was the chief guest of the evening, spoke on "Chirrhosis".

MALEGAON BRANCH—A meeting of the branch was held on 2-1-55. Dr. V. R. Gadgil, a member, was congratulated on his being elected as the chairman of the School Board Local Authority of Malegaon Municipal Burroughs.

MANDYA BRANCH—A meeting of the Executive Committee was held on 5-1-55. Seven members were present. Dr. H. Samasastry presided. Dr. B. Subbaraiah explained regarding the Eye Clinic to be conducted under the auspices of this branch.

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A meeting was held on 16-1-55. Thirty-five members were present. Dr. H. Samasastry presided. The members condoled the death of Dr. S. Subbarao, a founder member of the branch. Dr. B. Subbaramiah was elected the president of the branch. Dr. B. Subbaramiah delivered a lecture on "Infective Hepatitis and Wider Uses of I. V. Iron".

MATHURA BRANCH—An extra-ordinary meeting of the Branch was held on 17-12-54 with Dr. R. K. Garg in the chair. Dr. B. Gopal, Deputy Director, Medical and Health Services, U.P. and Dr. M. L. Mehrotra, Regional I/C of the B.C.G. team attended as guests. Dr. H. C. Rai, District Medical Officer of Health, Major Perhar of Combined Military Hospital, Mathura, Drs. Patancy and Jain of B.C.G. team also attended. Dr. B. Gopal spoke about B.C.G. scheme. Dr. Mehrotra gave details about the technical aspects of the scheme.

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An extra-ordinary meeting of the branch was held on 25-12-54. Eleven members were present. The following films were shown (1) Reorganisation and development of Medical relief in U.P., (2) Reforms in U.P. Jails and (3) Experiments in the revival of organism.

MORVI BRANCH—A meeting of the branch was held on 13-2-55. Dr. V. B. Mankad spoke on Conjunctivitis, Acute and Chronic and its treatment with antibiotic.

MUZAFFARNAGAR BRANCH—A meeting of the branch was held on 11-1-55 with Dr. V. Datt in the chair. Dr. J. L. Caroli addressed the meeting on "Infantile Cirrhosis of Liver".

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Dr. S. C. Sen and Dr. A. P. Mittra paid a visit to this branch on 13-2-55. Replying to the welcome address presented to him, Dr. S. C. Sen invited doctors to join the Association.

MORVI BRANCH—A meeting of the branch was held on 19-12-54. Dr. D. G. Dave spoke on "Truthfulness in Prognosis".

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A meeting of the branch was held on 6-2-55. Nine members were present. Dr. S. B. Shukla spoke on "Psychological Treatment and its Effects."

NALBARI BRANCH—The members of I. M. A. of Nalbari area met on 28-1-55 and considered the suitability of forming a separate branch at Nalbari. Dr. I. B. Rynjah presided. Nine members were present. It was decided to form the branch and accordingly the Assam State Branch was requested to recognise it. Dr. B. K. Goswami was elected the president for 1954-55 and Dr. G. Choudhury, the secretary.

NALGONDA BRANCH—A meeting of the branch was held on 4-2-55 with Dr. N. R. V. Swamy in the chair. Dr. N. R. V. Swamy spoke on "Head Injuries". Later Dr. K. Subba Rayudu presented a case of "Portal Cirrhosis—its differential diagnosis and treatment."

NIZAMABAD BRANCH—A meeting of the branch was held on 23-1-55. Dr. L. R. Deshpande presided. Dr. A. V. Subba Rao spoke on "Eruptive Fevers". Members of this branch conducted training classes in Health and Hygiene from 8-12-54 to 26-12-54.

NORTH MALABAR BRANCH—The annual general body meeting of the branch was held on 14-11-54. Office bearers were elected with Dr. (Major) T. K. Narayanan as president and Dr. P. K. Narayanan and Dr. (Mrs.) T. V. Meenakshi as hony. secretaries.

RANCHI BRANCH—The Republican Day Dinner was held on 26-1-55. Lt. General Sant Singh, G.O.C., Eastern Command was the chief guest.

PANDUA THANA BRANCH—A Rural Medical Conference was held on 16-1-55 under the auspices of the branch. Dr. A. K. Bose, president, Bengal Provincial Branch, I.M.A., presided. Dr. S. N. Roy, spoke on Surgical Emergencies, Dr. N. R. Konar on Cerebral Vascular Diseases, Dr. C. Ghosh on Obstetrical Emergencies, Dr. S. K. Panja on Modern Treatment of Tuberculosis (other than drug treatment), and Dr. P. K. Chatterjee on Modern Drug Treatment of Tuberculosis. Dr. A. K. Bose in his address discussed some of the medical problems of to-day and gave his advice regarding the difficulties of rural medical practice.

PORBANDAR BRANCH—A special meeting of the branch was held on 10-12-54 to meet Dr. P. R. Trivedi, the president of Gujarat and Saurashtra Provincial Branch. Dr. J. P. Sthanki was in the chair. Ten members were present. Dr. Trivedi in his speech discussed how to combat quackery. He also spoke on Rural Medical and Nutritional Surveys, Medical Inspection of School Children, and propagation of the sale of YOUR HEALTH. He also advised members to avail themselves of internship appointments. Dr. S. N. Mankad, Vice-president, West Zone spoke about social medicine.

* * * * *

A meeting of the branch was held on 26-12-54 with Dr. H. H. Chavda in the chair. Fourteen members were present. Dr. B. N. Joshi read a report of a case of chronic intestinal tuberculosis with x-ray pictures. A film on "Baby's First Year" was then shown.

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A Clinical meeting was held on 23-1-55 under the presidentship of Dr. H. H. Chavda. Twenty members were present. Dr. G. S. Nathwani read a case report of Delhi Boil. Dr. P. R. Pandya read a paper on "Psoriasis". Some medical films were also shown.

SALEM BRANCH—A meeting of the branch was held on 30-12-54 with Dr. S. Krishnamoorthy Rao in the chair. Dr. K. S. Krishna of Madurai spoke on 'Diseases of the Colon and Rectum'.

SHIMOGA BRANCH—A meeting of the branch was held on 8-1-55. Sri S. Sripadarao presided. A lecture in Kanada on Anaemia was given by Dr. B. R. Shama Rao. The meeting condoled the death of Dr. S. Subba Rao. Dr. D. Krishnamurthy spoke on the treatment of rabies. Dr. M. H. Srikantaiah read a case report on Chorea.

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A special committee of the branch discussed ways and means of carrying out the programme of a tuberculosis survey of the district. A questionnaire was proposed to be sent to all members to obtain the necessary information and send it to the secretary for compilation.

SHIMOGA BRANCH—A meeting of the branch was held on 5-2-55. Dr. S. Srinivasan was in the chair. A symposium on Acute Abdomen was held. Many of the members participated in the discussion.

SHOLAPUR BRANCH—A symposium on Diphtheria was arranged on 20-11-54 in which the prominent members took part.

* * * * *

A meeting was held on 8-1-55 when many interesting cases were discussed. An outdoor trip was arranged on 6-2-55 which proved a pleasant function.

SULTANPUR BRANCH—Office-bearers for 1954-55 were elected with Dr. P. C. Tandon as president and Capt. S. Banik as secretary. The annual report for 1953-54 shows that 6 general meetings were held during the year. Scientific discussions were held on some clinical cases.

TENALI BRANCH—A meeting of the branch was held on 23-1-54. Dr. K. V. Narasinharao presided. Dr. C. Krishnaiah demonstrated a case of Amoebic Liver Abscess. A symposium on E.N.T. Diseases and Emergencies was introduced. Dr. G. Lakshmipathy, Dr. N. Govindarajulu, Dr. M. Jagan Mohanrao, Dr. Ramachandra Reddy, Dr. C. Krishnaiah and and Dr. K. V. Narasinharao participated in it.

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At a meeting of the branch Dr. T. K. Krishnakuthy of General Hospital, Madras, spoke on "Cardiovascular Emergencies".

TIRUCHY BRANCH—A meeting of the branch was held on 23-1-55. Dr. N. C. Subramanyam presided. Thirty-two members were present. The members requested the Municipal authorities to take more energetic measures to eradicate the mosquito nuisance. Dr. V. S. Subramanyam gave a talk on "Allergy in E.N.T. Diseases". A film on Peridural Anaesthesia with Xylocaine was shown.

TIRUCHIRAPALLI DISTRICT BRANCH—A meeting of the branch was held on 11-12-54 with Dr. N. C. Subrahmanyam in the chair. Thirty-five members were present. Dr. C. Gopalan, Director, Nutrition Research Laboratory, Coonoor, gave a talk on Nutrition in Medicine and Surgery.

TIRUNELVELI BRANCH—A meeting of the branch was held on 27-11-54. Fifty members were present. Dr. A. S. Krishnan spoke on "Respiratory Infections in Children", with a demonstration of some X'rays. Dr. Kameswaran supplemented the lecture by some observations on "Acute Trached Bronchities in Children".

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An extra-ordinary meeting of the branch was held on 23-12-54. Forty-nine members were present. Col. Sangham Lal, Director of Medical Services, Madras, spoke on "Improving the standard of Medical Aid". An interesting discussion followed in which it was suggested that District Libraries should be provided with up to date books, medical bulletins be made available to all registered medical practitioners for a fee, laboratory facilities in hospital be made available to private doctors and provincialisation of the entire L.P. medical services.

VERAVAL-PATAN BRANCH—A meeting of the members of the medical profession of Veraval was held on 11-12-54 under the presidentship of Dr. P. A. Parekh, and a branch was opened and Dr. R. G. Tauna, the hony. secretary was authorised to take all necessary steps in this connection.

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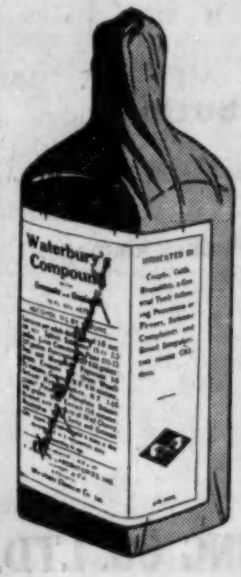

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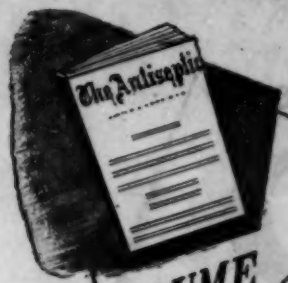

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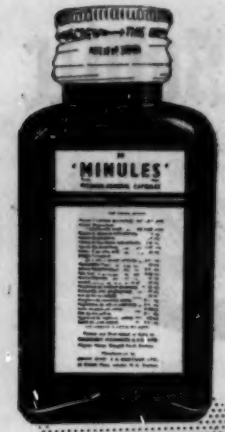

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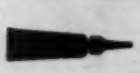
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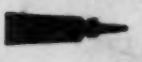
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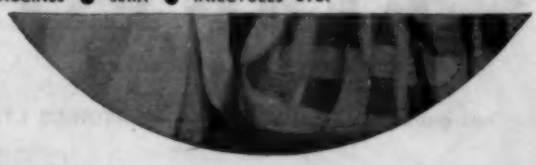

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